Fatigue at the interface between body and mind in chronic heart failure patients

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in het openbaar te verdedigen ten overstaan van een
door het college voor promoties aangewezen commissie
in de aula van de Universiteit
op vrijdag 2 oktober 2009 om 14:15 uur

door Otto Robert Frans Smith
geboren op 21 april 1978 te Emmen

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UITNODIGING

Graag nodig ik u uit voor
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Fatigue at the interface between body and mind in chronic heart failure patients

op vrijdag 2 oktober 2009
in de aula van de
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Warandelaan 2, Tilburg

Inleiding: 14:00 uur
Academische zitting:
14:15-15:15 uur

Aansluitend is er een receptie
ter plaatse.

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CONTENTS

CHAPTER 1:

General introduction

Heart failure (HF) can be defined as a syndrome in which patients generally display shortness of breath and fatigue, show signs of fluid retention, and have objective abnormalities in the structure and/or functionality of the heart (1). Additional terms to characterize heart failure patients include acute vs. chronic, and diastolic vs. systolic. Acute refers to a recent onset and transient state of HF, whereas chronic refers to a persistent condition of HF in which the patient is in a stable, worsening, or decompensated state. Patients with diastolic HF have symptoms of HF with a preserved left ventricular ejection fraction. Systolic refers to an impaired left ventricular pump function (left ventricular ejection fraction – LVEF) of the heart. A typical, but arbitrary cut-off for LVEF is 40 percent (1). This thesis focuses on chronic systolic heart failure (CHF).

The symptoms and signs of HF are the key to early detection because that is what causes patients to seek medical attention. Fatigue is a very important sign of HF, and is often rated as the most disabling symptom in HF (2). Nevertheless, fatigue in HF is poorly understood, is underreported in the cardiovascular literature, and is seldom a target for intervention (3-6). Hence, more research in this area is needed.

Standard HF treatment involves the prescription of a diuretic (to control fluid retention), an angiotensin-converting enzyme (ACE) inhibitor (to lower blood pressure), a beta-blocker (to slow down heart rate and lower blood pressure), a angiotensin II receptor antagonists (to control blood pressure), and aldosterone antagonist (for its diuretic effects). Sometimes digoxin is added to improve the pump efficiency of the heart. Some heart failure patients may require surgery, such as coronary artery bypass graft (CABG) surgery or heart valve repair, to improve damage to the heart or implantable devices to control irregular heart rhythms or to resynchronize the heart. As a last resort, patients with severe heart failure who do not respond to standard treatment may be eligible for a heart transplant (1,7).

The prevalence of HF increases with age. Epidemiological studies have shown that the population prevalence of HF is between 2 and 3 percent with a large increase after 75 of age up to 10-20 percent (8,9). The prevalence of HF has increased over the last decades as a result of the ageing of the population, and improved treatment and secondary prevention of coronary artery disease,

which is the most common cause of HF. Despite improved treatment modalities, HF mortality rates remain high, with 50 percent dying within 4 years (1,10).

Predicting HF prognosis remains challenging due to variations in etiology, treatment, and individual progression. Traditional risk factors (e.g. higher age, hypertension, low LVEF) are only able to predict a moderate proportion of the variance in mortality (11). Hence, exploring relatively understudied determinants is warranted with psychosocial factors being an interesting venue for study (12). In addition, patient-centered outcomes have gained importance because, from a patient's perspective, health status is generally as important as prolonged survival (13-18).

Psychosocial factors in CHF

So far, studies have primarily focused on the role of depression in CHF (19-23). Depression has been associated with an increased risk of mortality and poor health status, and this adverse effect has been found to be consistent across studies (23). Other psychosocial factors that have been studied in the context of CHF are anxiety, social support, and Type D personality. Mixed results have been reported for anxiety as a predictor of mortality (19,21,24), whereas stronger evidence was found for low social support as a predictor for poor CHF outcome (25,26).

Recently, the role of Type D personality, a joint tendency towards negative affectivity and social inhibition (27), has been studied in CHF (15-17,28-32). Schiffer et al. found that Type D personality was an independent predictor of respectively anxiety (30), depressive symptoms (17), health status (16), and cardiac mortality in CHF (31).

Vital exhaustion

A psychological factor that has been overlooked in the context of CHF thus far is vital exhaustion (VE). Vital exhaustion has three defining characteristics: feelings of excessive fatigue and lack of energy, increasing irritability, and feelings of demoralization (33,34). The concept of vital exhaustion was constructed as a result of the notion that patients with a myocardial infarction (MI) often report feelings of unusual tiredness and

malaise in the period prior to the MI (35). Several studies have shown that vital exhaustion predict coronary events in initially healthy persons (34,36), as well as in patients with established coronary artery disease (37,38).

Several potential (physiological) mechanisms have been studied to explain the relationship between vital exhaustion and adverse coronary events. The results of these studies suggest that exhausted subjects are characterized by: lower values of morning cortisol (39), lower levels of adrenocorticotropic hormone (40,41), increased blood coagulability together with a decreased fibrinolysis (42,43), higher levels of the cytokines IL-1β, IL-6, and TNF-α (44), higher levels of C-reactive protein (45), an increased number of leukocytes (45), higher antibody titers for cytomegalovirus (44), higher antibody titers for chlamydia pneumoniae (44), a higher viral load (46), a reduced amount of deep sleep (47), decreased heart rate variability (48), and lower concentration of macrophage migration inhibitory factor (49). It is concluded that vital exhaustion is associated with decreased activity of some important recovery mechanisms in combination with heightened inflammation (35).

The gold standard to determine whether a variable holds a causal relationship with an outcome variable is to conduct a randomized clinical trial. Therefore, the Exhaustion Intervention Trial (EXIT) was designed to evaluate the impact of a behavioral intervention on vital exhaustion and subsequent prognosis. Although the intervention had a beneficial effect on feelings of exhaustion, it could not be demonstrated that the intervention reduced the risk of a new coronary event within 2 years (50). Hence, there is currently no evidence that vital exhaustion qualifies as a modifiable risk factor in patients with coronary artery disease. Similar conclusions were drawn in related trials that focused on depression (51-53).

Vital exhaustion has sometimes been criticized for its overlap with depression and for its definition (54-56). It has even been argued that depression and vital exhaustion are interchangeable (55), although empirical support for that point of view is limited (54,56,57). The Maastricht Questionnaire (MQ), the primary tool to assess vital exhaustion, was originally designed to assess feelings of excessive fatigue, increasing irritability, and demoralization. However, this measure has also been shown to be closely

related to symptoms of fatigue, symptoms of depression, sleep problems, and lack of concentration (54).

Within the framework of CHF, little research has been performed on the role and nature of vital exhaustion. Still, specifically in CHF patients, studying its association with fatigue, one of the core symptoms of CHF, may lead to new insights with respect to disease progression (1,7).

Symptoms of fatigue in CHF

Characteristic symptoms of CHF are breathlessness, tiredness, and fatigue (1). Although it is widely acknowledged that fatigue is an important symptom of CHF, from a research perspective it has received little attention. Recent studies have underlined the importance of symptoms both in terms of prognosis (58,59) and health status (60), with fatigue often rated as one of the most disabling symptoms in chronic heart failure (2). In addition, it was shown that self-assessed symptoms and New York Heart Association (NYHA) classification were not coherent (61), indicating that there was little agreement between the patient and physician rated CHF symptoms. Self-assessed fatigue may therefore provide useful additional information about the patients' clinical and prognostic status.

Fatigue in CHF is not yet fully understood. Haemodynamically, symptoms of fatigue during exercise are thought to arise from failure of muscle perfusion due to an inadequate rise in cardiac output. However, many studies have shown that there is no relation between cardiac performance and exercise performance (4,5). Recently, it has been suggested that chronic, low grade haemodynamic stress as seen in CHF, may lead to dominance of catabolic processes. This in turn leads to skeletal myopathy, causing the sensation of fatigue (62). So far, there is limited empirical evidence to fully support this hypothesis.

Predicting fatigue in CHF has proven to be difficult and few studies have focused on this. Only one small study in 75 women with HF specifically addressed this issue and found that symptoms of dyspnoea were associated with fatigue (3). Hence, more studies are needed to get better insight into its predictors. The dynamic nature of fatigue warrants the investigation of these symptoms prospectively over time. Efforts should be made to obtain knowledge

about subgroups of CHF patients that are at increased risk to develop worse fatigue status over time, thereby providing an opportunity for risk stratification and prevention. Moreover, the prognostic impact of changes in self-reported fatigue should be examined as well.

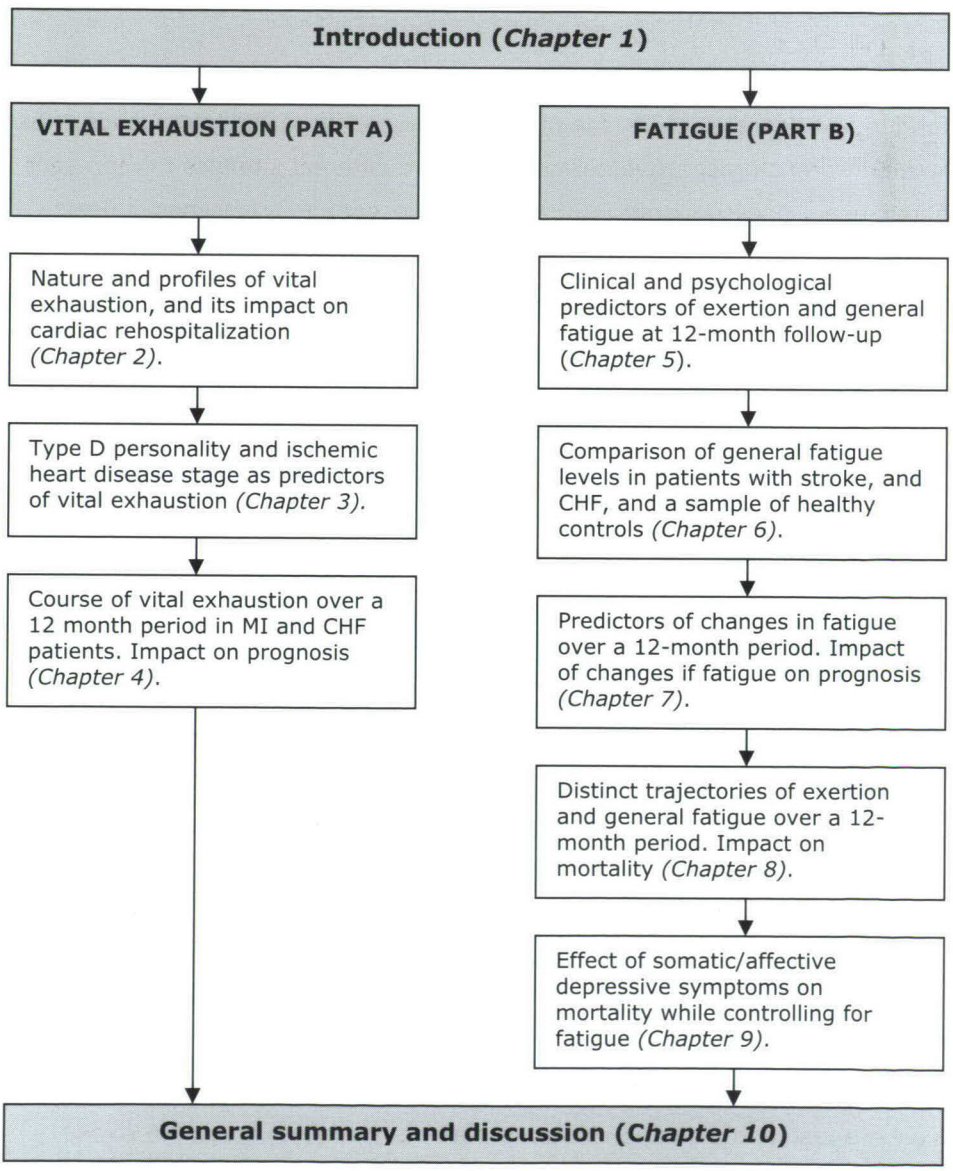
An important issue of studying psychological factors in heart disease is to examine the degree of distinctiveness between overlapping constructs to avoid redundancy and to promote efficient determination of patients with high-risk profiles (63). The experience of fatigue might depend on several coexisting conditions and factors that could be of relevance for disease progression (61). For instance, depression is common in heart failure patients and has been associated with poor outcome (23). Therefore, investigating the interrelationship between fatigue and depression in the context of CHF is needed.

Aim of the present thesis

This thesis presents the results of several studies. Most findings are based on an ongoing longitudinal study examining the role of psychological factors in CHF. Patients were recruited from the TweeSteden Hospital in Tilburg and Waalwijk, the Netherlands. Psychological, demographic, and clinical variables were collected at baseline, 2-, 6-, 12-, and 18-months follow-up. The research protocol was approved by the local medical ethics committee, and the study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from every patient. The chapters described in this thesis are based on data from this study, except for chapter 3, 4, and 6. These chapters also use data from other studies. Chapter 3 is partly based on 419 consecutive percutaneous coronary intervention (PCI) patients recruited in a study at the Erasmus Medical Center Rotterdam, the Netherlands (64). Chapter 4 is partly based on 407 patients that were recruited as part of the DepreMI study (65), which is a naturalistic follow-up study on the impact of depressive symptoms on cardiac prognosis in MI patients in four hospitals in the North of the Netherlands. Finally, chapter 6 is partly based on 80 consecutive stroke patients recruited at nursing home "De Hazelaar", Tilburg, the Netherlands, and 160 healthy controls from the general Dutch population.

As mentioned before, both vital exhaustion and fatigue have received little attention in the context of CHF. Therefore, the overall aim of this thesis was to examine the nature, course, and prognostic impact of vital exhaustion and fatigue in CHF patients. Figure 1 shows a schematic presentation of the outline of the thesis.

Figure 1. Outline of thesis



Outline of the thesis

Part A: Vital exhaustion

The first part of this thesis focuses on vital exhaustion. In a prospective study, principal component analysis was used to determine the structure of vital exhaustion in patients with CHF. The derived components were used to identify subgroups with different symptom profiles applying latent class cluster analysis. Subsequently, the impact of the symptom profiles on health status and cardiac rehospitalization at 6-month follow-up was investigated **(chapter 2).**

In **chapter 3**, the effect of ischemic heart disease stage on symptoms of fatigue and depression, i.e. the primary components of vital exhaustion, was examined using a prospective design, using two different samples to represent ischemic heart disease stage: PCI patients representing early ischemic heart disease stage, and CHF patients representing end-stage ischemic heart disease. In addition, the impact of Type D personality on fatigue and depression was evaluated.

A third study on vital exhaustion includes a sample of MI and CHF patients to investigate the course and characteristics of vital exhaustion over a 12-month period. The different trajectories of vital exhaustion extracted using latent class growth modeling were used to examine their effect on cardiovascular prognosis **(chapter 4)**.

Part B: Symptoms of fatigue

The second part of this thesis focuses on symptoms of fatigue. In line with previous research (66), two different measures of fatigue are used throughout these chapters: 1) The Dutch Exertion Fatigue Scale which measures fatigue directly related to performing of activities in daily living, and the Fatigue Assessment Scale which measures an overwhelming, sustained sense of fatigue that does not necessarily have a relationship with exertion.

Predictors of fatigue in CHF are largely unknown. Therefore, the aim of **chapter 5** was to examine clinical and psychological predictors of fatigue in CHF using a prospective design.

In **chapter 6**, the psychometric properties of the Fatigue Assessment Scale were tested in a sample of stroke patients. Levels of fatigue in stroke

have so far only been compared to healthy controls and patients with multiple sclerosis. Since stroke is a vascular disease, it is interesting to compare levels of fatigue to cardiac patients as well. Therefore, levels of general fatigue were compared as reported by stroke patients, CHF patients, and healthy controls.

Levels of fatigue are not necessarily stable over time. The dynamic nature of fatigue warrants the investigation of these symptoms prospectively. The aims of the study presented in **chapter 7** were to determine clinical, demographic, and psychological predictors of changes in fatigue over a 12-month period and to examine whether these changes in fatigue are predictive of adverse cardiac events occurring beyond 12 months.

In **chapter 8**, a similar approach is adopted as in chapter 4 to study the course of exertion and general fatigue over a 12-month period. Different trajectories of fatigue were derived using latent growth mixture modeling. Next, these different trajectories were linked to mortality beyond 12 months.

The last study presented in this thesis adds to a recent study of Schiffer et al. (67) which showed that somatic/affective rather than cognitive/affective symptoms of depression predict mortality in CHF. Since fatigue is highly prevalent among CHF patients and fatigue is a core characteristic of the somatic/affective domain of depression, the aim of **chapter 9** was to examine whether fatigue may explain away the relationship between somatic/affective symptoms of depression and mortality in CHF patients.

Finally, main outcomes, strengths and weaknesses of the studies are discussed in **chapter 10**. Recommendations for future research as well as for clinical practice are provided.

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CHAPTER 2:

Vital exhaustion in chronic heart failure: Symptom profiles, and clinical outcome

Otto RF Smith, Yori Gidron, Nina Kupper, Jobst B Winter, Johan Denollet
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ABSTRACT

Objective: The aim of this study was to examine the components of vital exhaustion (VE) in chronic heart failure (CHF) patients, and to examine whether psychological symptom profiles based on these components are differently associated with health status and cardiac rehospitalization. **Methods:** Consecutive CHF patients (N=381) were assessed for VE at baseline using the Maastricht Questionnaire (MQ) and for health status by means of the Minnesota Living With Heart Failure Questionnaire (MLWHFQ) at 6-month follow-up. Information on cardiac rehospitalization was obtained from the patients medical record. **Results:** Principal component analysis revealed 4 essential features of VE: Fatigue, cognitive-affective depressive symptoms, sleep difficulties, and lack of concentration. Latent class cluster analysis using these components identified 3 subgroups with different symptom profiles: A subgroup without VE, a first vitally exhausted subgroup (VE1; fatigue, lack of concentration, but with relative absence of cognitive-affective depressive symptoms and sleep difficulties), and a second, more severe, vitally exhausted subgroup (VE2; elevated levels on all components). Both vitally exhausted subgroups were more likely to have impaired health status (VE1: β=.36, p<.001; VE2: β=.71, p<.001). VE2 was also associated with increased risk for cardiac rehospitalization at 6-month follow-up (OR=2.98; 95%CI 1.01-8.83, p=.049). **Conclusions:** VE in CHF comprised 4 components (fatigue, cognitive-affective depressive symptoms, sleep difficulties, and lack of concentration) from which 3 different symptom profiles were derived. Subgroups with symptoms of vital exhaustion were associated with adverse clinical outcome in CHF. In clinical practice, these results may help identify distinct groups of patients with potentially differential risks of adverse health outcomes.

INTRODUCTION

Fatigue and vital exhaustion (VE) are frequently reported symptoms in patients with coronary artery disease and chronic heart failure (CHF) (1-3). The most commonly used definition of VE is that of unusual tiredness, increased irritability, and feelings of demoralization (4). VE has been associated with a 2 to 3 fold increased risk of mortality and morbidity in patients with coronary artery disease (2,5), and several potential biological pathways have been identified to explain this association. Vital exhaustion has been shown to relate to increased lipid metabolism (6), hypocortisolemia (7,8), reduced fibrinolytic capacity (9,10), parasympathetic withdrawal (11), and increased levels of cytokines, e.g. IL-6 (12,13).

The 21-item Maastricht Questionnaire (MQ) is often used to assess VE (4). Previous studies have shown that VE as measured by the MQ is not a unidimensional construct, but comprises different factors such as symptoms of fatigue, depressive symptoms, sleep problems, and lack of concentration (14-16) Nonetheless, in most studies, the total score was computed and subsequently dichotomized using a standardized cut-off of 14 in order to classify patients as either *vitally exhausted* or *not vitally exhausted* (17).

As a consequence, it is not fully understood what components of VE account for the association with clinical outcome in cardiac patients. One study in healthy men reported that, in a multivariate model, it was the fatigue subscale, and not the depression or irritability subscale, that predicted incident myocardial infarction (18). A few other studies examined the overlap between VE and depressive symptoms. In a large-scale study of Kopp et al. (19), VE and depressive symptoms were differently related to relevant external criteria suggesting that the constructs are distinct from each other. Furthermore, VE and depression shared less than 40 percent of the variance. The latter result was confirmed by Kudielka et al. (14), and McGowan et al. (15). However, a study by Wojciechowski et al. (20) found no support for the hypothesized separate conceptual identity of depression and vital exhaustion.

Next to studying components, it is also important to examine symptom profiles. Kubzansky et al. (21) recently stated that identification of risk profiles across the spectrum of symptoms and syndromes characterizing psychological discomfort, including subsyndromal conditions, might increase the sensitivity of

epidemiological prediction models and clarify the pathophysiological pathways linking negative psychological states to cardiac disease. In the context of VE, it would therefore be interesting to determine whether psychological symptom profiles based on the underlying components of VE are differentially related to clinical outcomes in CHF patients.

The objectives of the present prospective study were 1) to examine the components of vital exhaustion in CHF patients, and 2) to examine whether psychological symptom profiles based on these components are differently associated with health status and cardiac rehospitalization.

METHODS

Patients and design

The sample included 381 CHF patients, with systolic heart failure and a left ventricular ejection fraction (LVEF) ≤40%, visiting the heart failure outpatient clinic of the Twee Steden Hospital, Tilburg, the Netherlands. Patients with diastolic heart failure, age ≥80 years, myocardial infarction in the month prior to inclusion, other life-threatening diseases, and no or insufficient understanding of spoken and written Dutch language were excluded.

The design of the study was prospective, with patients completing a questionnaire assessing VE at baseline and health status at 6-month follow-up. The study protocol was approved by the local medical ethics committee in Tilburg, the Netherlands. The study was conducted conform to the Helsinki Declaration and every patient provided written informed consent.

Demographic and clinical variables

Demographic variables included sex, age, education, and marital status. Clinical variables comprised LVEF, NYHA class, etiology of CHF, co-morbidity (hypertension, diabetes, stroke, COPD, renal disease, liver disease), cardiac history (MI, PCI, CABG), cardiac medication, and body mass index (BMI). Information on clinical variables was obtained from the medical records and from the treating cardiologist.

Vital Exhaustion

VE was assessed by the 21-item Maastricht Questionnaire (4). Each item is rated according to a three-point scale (*Yes*=0; *?*=1; *No*=2), with a scale score obtained by summing the answers. The reliability of the total scale is good with Cronbach's alpha of 0.89 (5).

Endpoints at 6-month follow-up

Endpoints in this study were health status and cardiac rehospitalization at 6-month follow-up. The Minnesota Living with Heart Failure Questionnaire (MLWHFQ), a disease-specific instrument, was used to assess patient-rated health status at baseline (for control purposes) and follow-up (22). This questionnaire consists of 21 items that are answered on a four-point Likert scale. The reliability of the scale is good with Cronbach's alpha of 0.95 (22). A higher score on the MLWHFQ represents a poorer health status. The MLWHFQ is a frequently used measure to assess health status in CHF patients (23). Patients' hospital medical records were used to assess whether patients had been readmitted for cardiovascular causes between baseline and 6-month follow-up.

Statistical analyses

Principal component analysis (PCA) with oblimin rotation was used to determine the underlying structure of the MQ. Kaiser's criterion was adopted to identify the number of components, and subsequent KMO (Kaiser-Meyer-Olkin-Criteria) and Bartlett's test of sphericity were applied as fit indices. The resulting components were used to construct homogeneous subscales of VE. For each subscale, those items with the component loadings >.40 and cross loading differences >.20 were selected. Subscale homogeneity was examined by cronbach's alpha.

Identification of groups was obtained through latent class (LC) cluster analysis. LC cluster analysis is a state-of-art model-based clustering approach that has some important advantages over standard cluster analysis techniques. In LC cluster analysis, the cluster criterion is less arbitrary, no decisions have to be made about the scaling of the observed variables, and there are more formal criteria to make decisions about the number of clusters (24). In the

present study, we assumed that all the within-cluster covariances were zero (local independence), and the Bayesian Information Criterion (BIC) was used to determine the optimal number of clusters.

For comparison between groups we used the chi-square test for discrete variables. Adjusted standardized residuals were used to identify groups responsible for significant differences. A residual greater than 2.0 was taken to indicate a significantly higher frequency, and a residual less than -2.0 was considered to indicate a significantly lower frequency (25). In case of continuous variables, analysis of variance (ANOVA) was adopted. Multivariate ANOVA was employed to examine differences on subscale measures between groups identified by cluster analysis. The Student-Neuman-Keuls test was used for post-hoc analysis. Multiple regression analysis was used to assess the relationship between group membership and health status at 6-month follow-up, whereas logistic regression was used to assess the impact of group membership on rehospitalization at 6-month follow-up. The assumptions for multiple linear regression and logistic regression were checked and met. The LC cluster analysis was performed with the LCA program Latent GOLD (26). All other data were analyzed using SPSS 14.0.2 for Windows.

RESULTS

Components of vital exhaustion

PCA revealed a 4-component solution in the underlying structure of the MQ (Table 1). KMO (0.91) and Bartlett's test of sphericity (χ^2 (210) = 2765, $p<.001$) indicated that PCA was adequate for these data. Items 6, 9, and 12 were excluded from further analyses. The subscales that were constructed from the PCA reflected, respectively, 'fatigue' ($\alpha=.84$), 'cognitive-affective depressive symptoms' ($\alpha=.83$), 'sleep difficulties' ($\alpha=.67$), and 'lack of concentration' ($\alpha=.61$). The labeling of the components was based on previous literature (15), and face validity.

All components were associated with impaired health status at 6-month follow-up ($.29 < r < .59$; $p<.001$). After controlling for the interrelatedness of these components, fatigue ($\beta=.44$; $p<.001$), cognitive-affective depressive symptoms ($\beta=.19$; $p<.01$), and sleep difficulties ($\beta=.10$; $p<.05$) remained significantly associated with impaired health status at 6-month follow-up.

Table 1. Components of vital exhaustion

Item	Loading	Content
Component 1: Fatigue		
5	.74	Do you have the feeling that you have not been accomplishing much lately?
8	.71	Do you lately feel more listless than before?
1	.71	Do you often feel tired?
14	.66	I feel fine (reverse).
15	.65	Do you feel that your body is like a battery that is losing its power?
17	.53	Do you have the feeling these days that you just do not have what it takes anymore?
4	.50	Do you feel weak all over?
9†	*.28*	*I enjoy sex just as much as I used to (reverse).*
Component 2: Cognitive-affective depressive symptoms		
13	.83	Do you feel you want to give up trying?
16	.81	Would you want to be dead at times?
18	.70	Do you feel dejected?
7	.64	Do you believe that you have come to a dead end?
19	.60	Do you feel like crying sometimes?
10	.55	Have you experienced a feeling of hopelessness recently?
6†	*.45*	*Do you have the feeling that you cannot cope with everyday problems as well as you used to?*
Component 3: Sleep difficulties		
2	.82	Do you often have trouble falling asleep?
3	.78	Do you wake up repeatedly in the night?
20	.57	Do you ever wake up with a feeling of exhaustion and fatigue?
Component 4: Lack of concentration		
11	.82	Does it take you more time to grasp a difficult problem than it did a year ago?
21	.78	Do you have increasing difficulty in concentrating on a single subject for long?
12†	*.39*	*Do little things irritate you more than they used to?*

† Items with component loadings <.40 or cross loading differences <.20 were excluded from further analyses.

Furthermore, fatigue (OR=1.04; 95%CI 1.00-1.08, $p<.05$) and cognitive-affective depressive symptoms (OR=1.03; 95%CI 1.00-1.06, $p<.05$) were associated with cardiac rehospitalization at 6-month follow-up in bivariate

analysis. However, after controlling for their interrelatedness, both components became non-significant.

Profiles of vital exhaustion

As shown in Table 2, a solution with three patient clusters resulted in the lowest BIC-value. Figure 1 visualizes the three VE profiles. Cluster 1 (24.1%; n=92) is characterized by a relative absence of VE, and is therefore labeled the 'No VE group'. Cluster 2 and 3 can both be labeled as groups with manifest symptoms of VE. Cluster 2 (47.2%; n=180) is characterized by increased levels of fatigue and decreased concentration, but also by a relative absence of cognitive-affective depressive symptoms and sleep difficulties. Although the differences between cluster 1 and 2 with respect to cognitive-affective depressive symptoms and sleep difficulties were statistically significant, the small to moderate effect sizes may indicate lack of clinical significance, supporting our characterization of cluster 2. Finally, cluster 3 (28.6%; n=109) is characterized by the presence of manifest symptoms of VE, including cognitive-affective symptoms of depression and sleep difficulties.

Table 2. Model clusters and diagnostic indices

Model	LL†	BIC (LL)	ΔBIC (LL)‡	Parameters	Df
1 cluster	-2868	5950	-	36	345
2 cluster	-2727	5698	-252	41	340
3 cluster	-2702	5678	-20	46	335
4 cluster	-2698	5698	20	51	330
5 cluster	-2692	5717	19	56	325
6 cluster	-2688	5738	21	61	320

† LL = log likelihood
‡ ΔBIC (LL) = BIC {more complex model} – BIC {simpler model}, a negative value indicates that improved model fit outweighs increased model complexity

Cluster characteristics are shown in Table 3. Based on the adjusted standardized residuals, patients in cluster 1 were more likely to be male and to have no academic education, and less likely to have NYHA-class III/IV heart failure, comorbidities, diabetes, or diuretics treatment. Patients in cluster 3 were younger, and had a higher BMI compared with cluster 1 and 2.

Table 3. Demographic and medical characteristics stratified by cluster membership

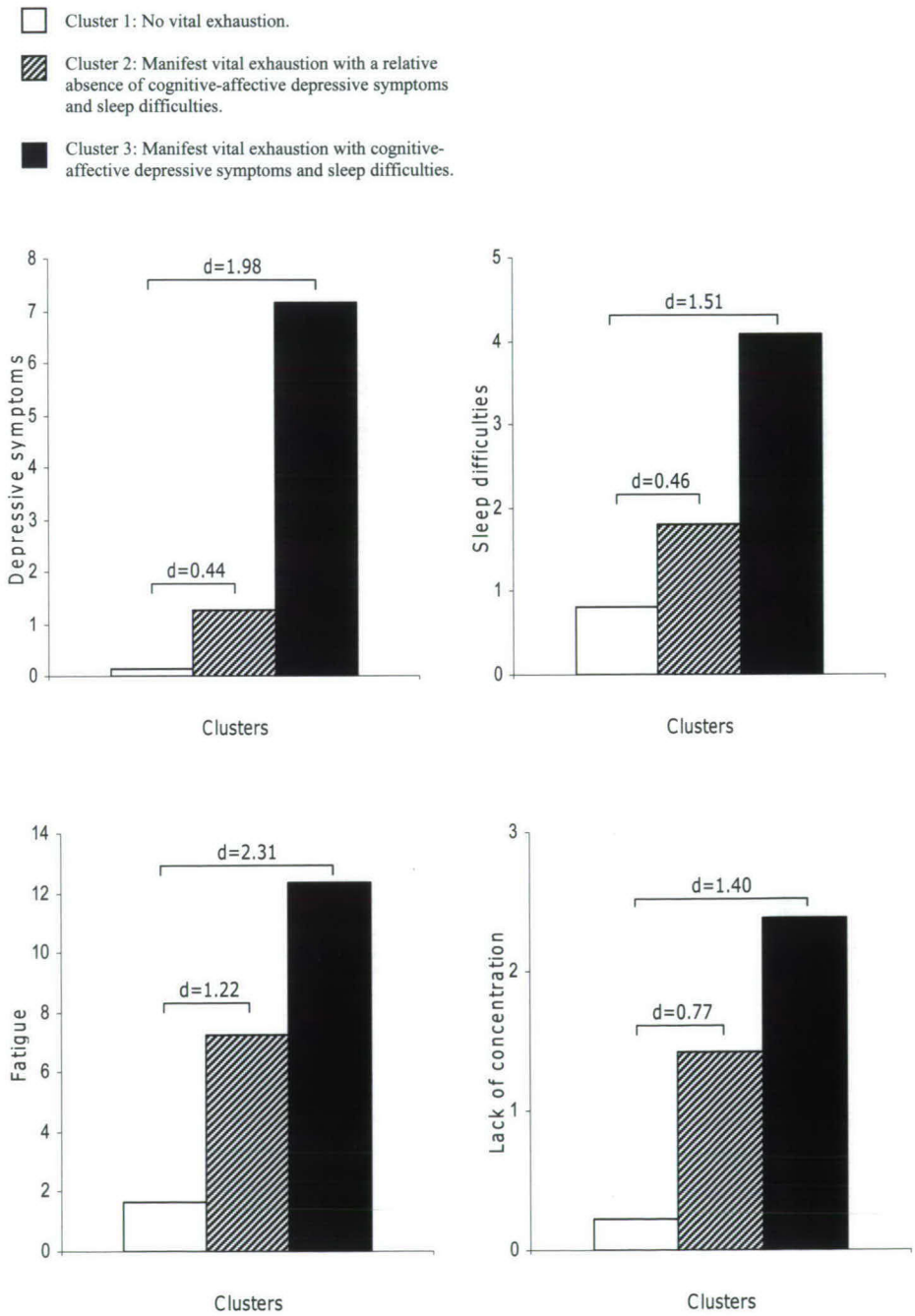
	Total sample	Cluster 1* (n=92)	Cluster 2* (n=180)	Cluster 3* (n=109)	*p*-value
Age, mean (SD)	**65.7 (10.4)**	66.6 (9.7)	66.7 (10.6)	63.5 (10.4)	.03
Male sex, % (n)	**72.2 (275)**	81.5 (75)	73.3 (132)	62.4 (68)	.009
Having a partner, % (n)	**72.2 (275)**	79.3 (73)	74.4 (134)	62.4 (68)	.02
No academic education, % (n)	**85.8 (327)**	78.3 (72)	87.2 (157)	89.9 (98)	.05
NYHA-class III/IV, % (n)	**39.6 (151)**	27.2 (25)	39.4 (71)	50.5 (55)	.003
LVEF: Mean (SD), mean (SD)	**30.8 (6.9)**	31.2 (7.5)	30.4 (6.8)	31.0 (6.4)	.65
Ischemic etiology, % (n)	**54.1 (206)**	51.1 (47)	53.9 (97)	56.9 (62)	.71
Cardiac history†, % (n)	**57.5 (219)**	55.4 (51)	56.7 (102)	60.6 (66)	.73
Smokers, % (n)	**23.9 (91)**	28.3 (26)	22.8 (41)	22.0 (24)	.52
Comorbidity‡, % (n)	**58.3 (222)**	46.7 (43)	62.8 (113)	60.6 (66)	.03
Diabetes, % (n)	**24.9 (95)**	16.3 (15)	25.6 (46)	31.2 (34)	.05
ACE-inhibitor, % (n)	**71.4 (272)**	70.7 (65)	72.2 (130)	70.6 (77)	.94
Diuretics, % (n)	**72.7 (277)**	59.8 (55)	73.3 (132)	82.6 (90)	.001
Digoxin, % (n)	**24.7 (94)**	23.9 (22)	27.8 (50)	20.2 (22)	.34
Beta blocker, % (n)	**66.9 (255)**	75.0 (69)	65.9 (118)	62.4 (68)	.17
Statins, % (n)	**50.9 (194)**	51.1 (47)	51.1 (92)	50.5 (55)	.99
Aspirin, % (n)	**40.9 (156)**	37.0 (34)	43.3 (78)	40.4 (44)	.59
BMI, mean (SD)	**28.1 (5.3)**	27.0 (4.9)	27.8 (4.4)	29.4 (6.6)	.005

* Cluster 1=no vital exhaustion; Cluster 2=vital exhaustion with relative absence of depressive symptoms and sleep difficulties; Cluster 3=vital exhaustion with depressive symptoms and sleep difficulties

† History of MI, CABG, PCI

‡ Stroke, COPD, hypertension, peripheral arterial disease, renal insufficiency

Figure 1. Symptom profiles of vital exhaustion[1]



[1] 'd' = Cohen's d (effect size); all shown comparisons were statistically significant (all $p<.05$)

In addition, cluster 3 contains relatively more females, more patients without a partner, more patients in NYHA-class III/IV, and more patients on diuretics than would be expected from the independence hypothesis.

Multivariate ANOVA revealed that there was an overall significant main effect for cluster membership on the components of VE (Wilks lambda=0.15; F (8,732)=145.1, p<.0001) adjusting for age, sex, marital status, educational level, NYHA-class, comorbidities, diabetes, diuretics and BMI. Only main effects and two-way interactions were included in the model. This finding indicates that differences between clusters on VE cannot be explained by the included covariates. Therefore, the clusters provide unique information on the identification of subgroups of vital exhaustion in patients with CHF.

Vital exhaustion profiles and health status

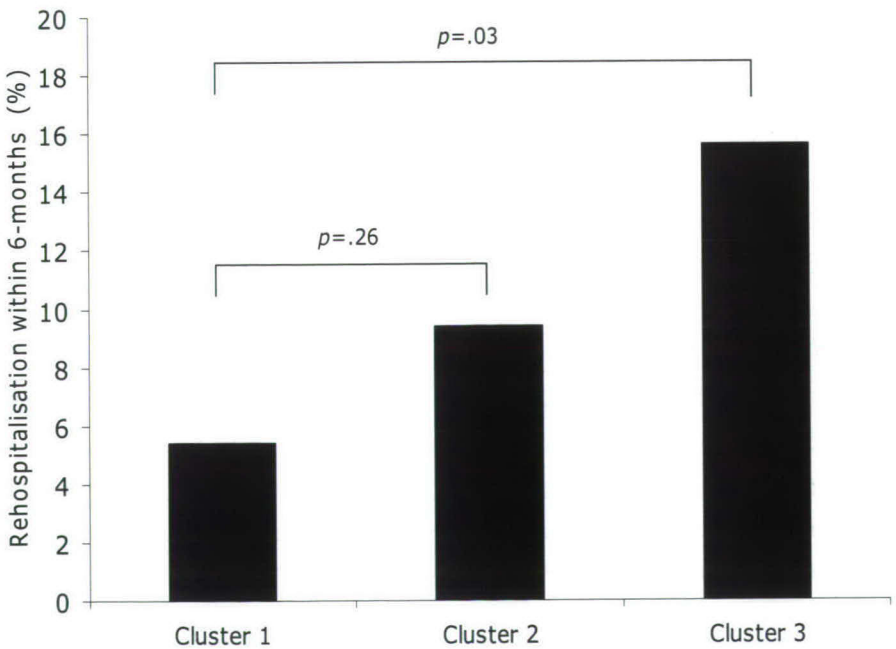
The mean level of impaired health status was the highest among patients in cluster 3 (M=44.5, SD=21.5); patients in cluster 2 (M=26.7, SD=15.9) also reported higher levels of impaired health status as compared to cluster 1 patients (M=11.6, SD=12.5; all $p<.001$). In multivariate analyses using cluster 1 as the reference category, health status was associated with exhaustion subtype after controlling for age, sex, marital status, educational level, NYHA-class, comorbidities, diabetes, diuretics and BMI. The VE group with cognitive-affective depressive symptoms and sleep difficulties (Cluster 3; $\beta=.71$, $p<.001$) and the VE group with a relative absence of cognitive-affective depressive symptoms and sleep difficulties (Cluster 2; $\beta=.36$, $p<.001$) were associated with impaired health status as compared to the no vital exhaustion subgroup. In addition, higher age ($\beta=.12$, $p<.05$) and NYHA-class ($\beta=.12$; $p<.05$) were also associated with impaired health status. Other variables were not associated with health status in multivariate analysis. After controlling for health status at baseline, exhaustion subtype (Cluster 3; $\beta=.27$, $p<.001$; Cluster 2; $\beta=.14$, $p<.01$) remained a significant predictor of impaired health status at 6-month follow-up.

Vital exhaustion profiles and cardiac rehospitalization

Over the period of follow-up, 39 patients (10.2%) were readmitted for cardiovascular causes. As displayed in Figure 2, vitally exhausted patients with

all symptoms, including cognitive-affective depressive symptoms and sleep difficulties (cluster 3) were more likely to be rehospitalized as compared to patients without VE (cluster 1). Vitally exhausted patients with a relative absence of cognitive-affective depressive symptoms and sleep difficulties (cluster 2) also showed a tendency to more hospitalizations as compared to patients in cluster 1, but this was not statistically significant. In multivariate logistic regression including the same covariates as in the previous section, cluster 3 was a significant predictor of cardiac rehospitalization at 6 month follow-up (OR=2.98; 95%CI 1.01-8.83, p=.049), whereas cluster 2 did not reach statistical significance (OR=1.77; 95%CI 0.62-5.03, p=.29).

Figure 2. Cardiac rehospitalization at 6-month follow-up stratified by clusters of vital exhaustion



DISCUSSION

The aim of the study presented here was to examine components of VE in CHF patients and the associations of symptom clusters with health status and cardiac rehospitalization at 6-month follow-up. Results showed that the underlying structure of VE consisted of four components: fatigue, cognitive-affective depressive symptoms, lack of concentration, and sleep difficulties. The labeling of the components was based on previous literature (15), and face validity. Fatigue, cognitive-affective depressive symptoms, and sleep difficulties were independently associated with impaired health status at 6-month follow-up. In addition, fatigue and depressive symptoms were associated with cardiac rehospitalization at 6-month follow-up in bivariate analysis.

Latent class cluster analysis based on the components of VE revealed three symptom clusters: a subgroup without manifest symptoms of VE, and two subgroups with manifest symptoms of VE characterized by presence of fatigue and lack of concentration. Importantly, one VE subgroup was characterized by a relative absence of cognitive-affective depressive symptoms and sleep difficulties, while the other VE subgroup had elevated levels on all components. Patients in the two VE subgroups were more likely to report impaired health status at follow-up as compared to the subgroup without VE. Furthermore, only the VE subgroup with cognitive-affective depressive symptoms and sleep difficulties (cluster 3) was an independent predictor of cardiac rehospitalization at follow-up. Vitally exhausted patients with a relative absence of cognitive-affective depressive symptoms and sleep difficulties (cluster 2) did however show a tendency to experience more events as compared to patients without VE, though this did not reach statistical significance.

The components of VE obtained in the present study are in line with previous research (14-16). Fatigue and cognitive-affective depressive symptoms accounted for the greatest part of explained variance in the MQ and therefore comprised the two predominant components of VE. We were however unable to show which of these two components is more important when it comes to predicting objective clinical outcome (i.e. rehospitalization). In fact, our findings suggest that it is the shared variance between fatigue and cognitive-affective depressive symptoms that predicts cardiac rehospitalization.

Obviously, it is too soon to draw firm conclusions about the exact role of fatigue and cognitive-affective depressive symptoms and their interrelationship in predicting cardiac outcome. Some studies suggest that fatigue has the strongest predictive power (18), whereas others put cognitive-affective depressive symptoms forward as the strongest predictor (16,27). Large-scale studies with long-term follow-ups and hard outcomes are necessary to come to more definite answers.

One of the interesting aspects of the present study was the cluster analytic approach. Instead of evaluating the predictive qualities of the individual components, cluster analysis enabled us to identify high-frequent symptom profiles within a given sample using all derived components. That means it focuses on clustering of psychological risk factors rather than focusing on a single risk factor. Such an approach was recently encouraged by Suls and Bunde (28). In fact, there needs to be more appreciation that the clustering and overlap of negative affective dispositions may make specificity of emotion less critical for cardiac risk. For example, fatigue and cognitive-affective depressive symptoms may both increase the risk of poor health outcomes because they share a general disposition to experience chronic and intense negative emotions. Kubzansky and colleagues (21) also argued that identifying various forms of distress, even in their less severe states, may provide an important avenue for early intervention. Effective treatment targeting psychosocial risk factors in CAD patients requires an accurate characterization of who is at risk for adverse outcomes. A more detailed examination of the symptom profiles may better inform the development of more effectively timed and more specifically tailored behavioral interventions.

The results of this study suggest that focusing on symptoms of depression alone may not be sufficient since patients with elevated levels of fatigue and lack of concentration, but with a relative absence of depressive symptoms and sleep difficulties, also had impaired health status at follow-up. In addition, this cluster showed a tendency to be associated with cardiac rehospitalization as well. This "subclinical" group can therefore be an interesting study target. An important next step is to evaluate the effect of this symptom cluster on cardiac mortality.

This study has a number of limitations. First, there may have been a bias in the selection of patients. The cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern might have influenced selection. Second, the follow-up period was relatively short and we did not include mortality as an endpoint. Third, we did not screen for major depression in this study and were therefore not able to control for the effect of major depression on cardiac prognosis. Our study also has a number of strengths, including the use of valid and reliable questionnaires, a state-of-the-art model-based clustering approach, and a prospective design to validate the derived clusters.

In conclusion, the underlying structure of VE can be characterized by fatigue, cognitive-affective depressive symptoms, sleep difficulties, and lack of concentration. Symptom profiles based on these features revealed a subgroup without VE and two subgroups with VE. Both VE subgroups were associated with impaired health status, despite the relative absence of cognitive-affective depressive symptoms and sleep difficulties in one of these subgroups. The subgroup with cognitive-affective depressive symptoms and sleep difficulties was at increased risk for cardiac rehospitalization. This study needs to be replicated in a similar sample with a longer follow-up using mortality as an endpoint. The profiles of VE based on the underlying structure reported here provide a basis for profile analysis of psychological symptom change in outcome studies with cardiac patients and are potentially valuable for both research and clinical practice.

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CHAPTER 3:

Symptoms of fatigue and depression in ischemic heart disease are driven by personality characteristics rather than disease stage: A comparison of CAD and CHF patients

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ABSTRACT

Background: Symptoms of fatigue and depression are prevalent across stages of ischemic heart disease (IHD). We examined (1) the effect of both the IHD stage and Type-D personality on fatigue and depressive symptoms at 12-month follow-up, and (2) whether the effect of type-D personality on these symptoms is moderated by IHD stage. **Methods:** Two different samples of patients were included to represent IHD stage: 401 PCI patients (early-stage IHD) and 105 ischemic CHF patients (end-stage IHD) completed the DS14 Type-D Scale at baseline. Logistic regression analysis was used to examine the impact of IHD stage and type-D personality on fatigue and depression at follow-up. **Results:** Disease stage was neither associated with symptoms of fatigue (p=.99) nor depression (p=.29) at 12 months. In contrast, type-D personality was shown to predict both symptoms of fatigue (OR=2.96; 95%CI 1.92-4.58, p<.001) and depression (OR=4.91; 95%CI 3.16-7.65, p<.001) at follow-up; the effect of type-D personality on these symptoms was not moderated by disease stage. In multivariable analysis, type-D remained a significant predictor of symptoms of fatigue (OR=3.14; 95%CI 1.98-4.99, p<.001) and depression (OR=5.90; 95%CI 3.60-9.67, p<.001), also after controlling for symptom levels at baseline. **Conclusion:** Type-D personality but not disease stage predicted symptoms of fatigue and depression at 12-month follow-up.

INTRODUCTION

Fatigue is prevalent across stages of ischemic heart disease (IHD). Symptoms of fatigue have previously been reported by patients with stable and unstable angina [1], myocardial infarction (MI) [2,3], and chronic heart failure (CHF) [4,5]. Although the prevalence of fatigue varies slightly, fatigue seems to be ubiquitous across IHD disease stages [1,3,4] and to persist despite adequate medical treatment. Similarly, depressive symptoms are common across disease stages, exerting a deleterious effect on health outcomes across these stages [6-8]. In clinical practice, knowledge of the determinants of fatigue and depressive symptoms is important for secondary prevention, given that they may influence the clinical course of IHD and CHF [7-10]. However, the determinants of symptoms of fatigue and depression are not clear yet.

In addition to IHD stage, personality may comprise a moderating factor of fatigue and depressive symptoms. The *distressed* (type-D) personality has been shown to predict fatigue in coronary artery disease (CAD) patients treated with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery [1,11], and the onset of depression in PCI patients [12,13], and is associated with depression in patients with CHF [14]. Type-D personality is defined as the tendency to experience negative emotions and to inhibit self-expression [15]. The objectives of the current study were two-fold: 1) To examine the effect of both the IHD stage and Type-D personality on fatigue and depressive symptoms at 12-month follow-up; 2) To determine whether the effect of type-D personality on fatigue and depressive symptoms is moderated by IHD stage.

METHODS

Participants and study design

We included two different samples of cardiac patients to represent ischemic heart disease stage, namely CAD patients treated with PCI to reflect early-stage heart disease and ischemic CHF patients to represent end-stage heart disease. The CAD patients comprised 419 consecutive patients with stable or unstable angina, treated with PCI at the Erasmus Medical Center Rotterdam using the paclitaxel-eluting stent as the default strategy. A more detailed description of this sample has been provided elsewhere [1]. Of 419

patients, 18 with a left ventricular ejection fraction (LVEF) ≤40% were excluded, as this is an indication for CHF, leaving 401 patients for further analyses.

The CHF sample comprised 105 ischemic patients visiting the heart failure outpatient clinic of the TweeSteden Hospital, Tilburg, the Netherlands. Inclusion criteria were systolic heart failure, LVEF ≤40%, and sufficient understanding of the spoken and written Dutch language. Patients with diastolic heart failure, age ≥80 years, myocardial infarction in the month prior to inclusion, other life-threatening diseases, or insufficient knowledge of the Dutch language were excluded. For this study, patients with non-ischemic aetiologies were also excluded. Of 135 patients, 11 died prior to 12-month follow-up and 19 were excluded due to missing questionnaire data at follow-up. All patients completed questionnaires at baseline and at 12-month follow-up.

The study protocol was approved by the medical ethics committee of the respective hospitals, and the study was conducted in accordance with the Helsinki Declaration. All patients provided written informed consent.

Demographic and clinical variables

Demographic variables included gender, age, and marital status (having a partner vs. not having a partner). Information on clinical variables, that is, disease stage (CAD *versus* CHF), previous cardiac history (MI, PCI, or CABG), hypertension, diabetes mellitus, smoking, and cardiac medication (aspirin, beta-blockers, diuretics, ACE-inhibitors, and statins) was obtained from the patients' medical records.

Symptoms of fatigue and depression

The Maastricht Questionnaire (MQ) was used to assess symptoms of fatigue and depression [10]. The questionnaire consists of 21 items that are answered on a three-point scale (0=no; 1=?; 2=yes). Research suggests that the MQ predominantly assesses two symptom dimensions, namely fatigue and depression [1,16]. We adopted the factor solution found in a previous study of the PCI patients included in the current study [1], which is similar to that found in a previous study [16]. The reliability of the subscales, as measured by

Cronbach's α, were .87 and .83, respectively. The MQ was administered both at baseline and at 12-month follow-up.

Type-D personality

We used the Type-D Scale (DS14) to assess the distressed (type-D) personality [17]. The scale consists of 14 items that are answered on a five-point Likert scale from 0 (false) to 4 (true). Seven items tap negative affectivity and seven items social inhibition (score range 0–28 for each subscale). Type-D caseness is defined by a high score on both subscales, as determined by a standardized cut-off score ≥10 [17]. The DS14 is a valid and reliable scale, with Cronbach's α of .88 and .86 and 3-month test–retest reliability of r =.72 and .82 for the negative affectivity and social inhibition subscales, respectively [17]. Type-D personality is more than negative affect, as it also takes into account how patients deal with this affect through the inclusion of the social inhibition component [12,17]. The DS14 was administered at baseline.

Statistical analyses

Discrete variables were compared with the chi-square test and continuous variables with Student's t test for independent samples. A McNemar's test was used to assess whether the prevalence of fatigue and depression changed between baseline and 12-month follow-up. Univariable and multivariable logistic regression analyses were used to examine the impact of IHD stage and type-D personality on fatigue and depression at 12-month follow-up. The moderating effect of IHD stage on the relationship between type-D personality and fatigue and depression, respectively, was examined by testing the interaction effect for type-D *by* IHD stage. Prior to analyses, the fatigue and depression subscale scores were dichotomized using the highest tertile to indicate clinically manifest symptoms. Dichotomization was used to enhance clinical interpretability, as advocated by others [18].

RESULTS

Baseline characteristics

As displayed in Table 1, CAD patients were more likely to suffer from hypertension and to be prescribed aspirin. On the other hand, CHF patients were older and more likely to be males, smokers, and diabetics. In addition, they were more likely to have a history of MI and CABG and to use β-blockers, ACE-inhibitors, and diuretics.

The prevalence of type-D in the CAD patients was 24.4% versus 22.9% in the CHF patients (p=.72). CAD patients with a type-D personality were more likely to use diuretics as compared to CAD patients without type-D. CHF patients with a type-D personality did not differ from non type-D CHF patients on demographic and clinical baseline characteristics (Table 1). No other statistically significant differences were found between type-D and non type-D CHF and PCI patients, respectively, on demographic and clinical baseline characteristics.

There was a significant decrease in the prevalence of symptoms of fatigue over time (35.6% at baseline vs. 28.6% at 12-month follow-up, p=.007). The prevalence of depressive symptoms was stable over time (36.6% at baseline vs. 33.6% at 12-month follow-up, p=.93).

IHD stage, type-D and symptoms of fatigue and depression

In univariable analysis, IHD stage was neither associated with symptoms of fatigue (p=.99) nor depression (p=.29) at 12-month follow-up. In contrast, type-D personality was shown to predict both symptoms of fatigue (OR=2.96; 95%CI 1.92-4.58, p<.001) and depression (OR=4.91; 95%CI 3.16-7.65, p<.001) at follow-up. IHD stage neither moderated the relationship between type-D personality and symptoms of fatigue (p=.70) nor depression (p=.27), as shown by the non-significant interaction effects. Hence, type-D personality had the same effect on fatigue and depression irrespective of IHD stage, that is whether patients were diagnosed with CAD or with CHF (Figure 1).

Similarly, multivariable analysis revealed that type-D personality, but not IHD stage, was an independent predictor of both symptoms of fatigue and depression. There was a near significant effect for smoking and hypertension

Table 1. Baseline characteristics

	CAD-patients (N=401)				CHF-patients (N=105)				
	Total	**Type-D (n=98)**	**Non type-D (n=303)**	***p***	**Total**	**Type-D (n=24)**	**Non type-D (n=81)**	***p***	***p*** *(total)*
Demographics									
Female gender, n (%)	**105 (26.2)**	25 (25.5)	78 (25.9)	.94	**20 (19.0)**	2 (8.3)	18 (22.2)	.11	**.03**
Age, mean (SD)	**62.9 (10.9)**	61.9 (10.2)	63.1 (11)	.33	**66.6 (8.8)**	69.4 (7.6)	65.7 (8.9)	.09	**.001**
Married/partner, n (%)	**331 (82.5)**	82 (83.7)	248 (81.8)	.76	**82 (78.1)**	20 (83.3)	62 (76.5)	.48	**.19**
Clinical									
Smoking, n (%)	**47 (11.7)**	11 (11.2)	36 (12)	.84	**22 (21.0)**	4 (16.7)	18 (22.2)	.56	**.01**
Hypertension, n (%)	**197 (49.1)**	51 (52)	145 (48.2)	.51	**39 (37.1)**	10 (41.7)	29 (35.8)	.60	**.03**
Diabetes, n (%)	**78 (19.5)**	22 (22.4)	54 (17.9)	.32	**30 (28.6)**	5 (20.8)	25 (30.9)	.34	**.04**
History of MI, n (%)	**154 (39.0)**	36 (37.5)	117 (39.8)	.69	**85 (81.0)**	21 (87.5)	64 (79)	.35	**<.001**
History of PCI, n (%)	**99 (24.7)**	23 (23.5)	76 (25.2)	.72	**28 (26.7)**	4 (16.7)	24 (29.6)	.21	**.68**
History of CABG, n (%)	**54 (13.5)**	12 (22.2)	42 (14)	.67	**51 (48.6)**	10 (41.7)	41 (50.6)	.44	**<.001**
Medication									
β-blockers, n (%)	**92 (22.9)**	22 (22.4)	69 (22.9)	.92	**77 (73.3)**	17 (70.8)	60 (74.1)	.75	**<.001**
ACE-inhibitors, n (%)	**34 (8.5)**	11 (11.2)	23 (7.6)	.27	**80 (76.2)**	18 (75)	62 (76.5)	.88	**<.001**
Diuretics, n (%)	**7 (1.7)**	5 (5.1)	2 (0.7)	.004	**85 (81.0)**	22 (91.7)	63 (77.8)	.13	**<.001**
Statins, n (%)	**304 (75.8)**	71 (72.4)	232 (77.1)	.35	**73 (69.5)**	18 (75)	55 (67.9)	.51	**.18**
Aspirin, n (%)	**386 (96.3)**	95 (96.9)	289 (96)	.68	**62 (59.0)**	14 (58.3)	48 (59.3)	.94	**<.001**

Table 2. Predictors of symptoms of fatigue and depression at 12-month follow-up (multivariable analysis)

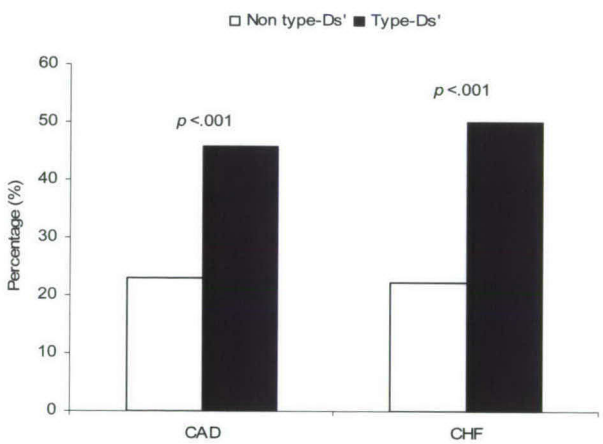
	Fatigue			Depression		
	Odds Ratio	**95% CI**	**p**	**Odds Ratio**	**95% CI**	**p**
Variables of interest						
IHD stage[1]	.45	.14-1.41	.17	*.30*	*.10-1.07*	*.07*
Type-D personality	**3.14**	**1.98-4.99**	**<.001**	**5.90**	**3.60-9.67**	**<.001**
Covariates						
Female gender	0.99	.58-1.68	.97	**.36**	**.21-.61**	**<.001**
Age	.99	.97-1.01	..29	**.97**	**.95-.99**	**.01**
Married/partner	1.58	.88-2.81	.13	1.48	.82-2.66	.19
Smoking	*1.75*	*.95-3.24*	*.07*	.94	.49-1.80	.85
Hypertension	*1.48*	*.95-2.31*	*.08*	.85	.54-1.34	.49
Diabetes	1.21	.71-2.05	.48	1.14	.66-1.96	.64
History of MI	1.24	.77-1.97	.37	*1.56*	*.97-2.52*	*.07*
History of PCI	1.19	.73-1.95	.49	1.04	.63-1.72	.89
History of CABG	.77	.42-1.41	.40	.79	.43-1.46	.44
β-blockers	1.14	.69-1.88	.60	1.23	.74-2.06	.42
ACE-inhibitors	1.29	.66-2.53	.45	**2.51**	**1.23-5.11**	**.01**
Diuretics	1.71	.58-5.06	.34	1.34	.42-4.27	.62
Statins	1.01	.61-1.65	.98	.39	.75-2.10	.39
Aspirin	.56	.26-1.19	.13	.77	.35-1.71	.52

[1] CHF = 1; CAD = 0

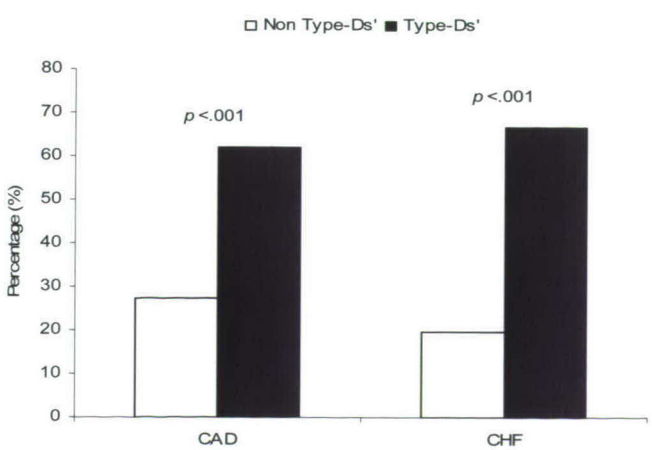
on symptoms of fatigue. Female sex, younger age, and use of ACE-inhibitors were associated with an increased risk of depressive symptoms at 12-month follow-up. Near significant effects were found for IHD stage and history of MI (Table 2). The effect of type-D personality on symptoms of fatigue (OR=1.87; 95%CI 1.12-3.15, p=.02) and depression (OR=3.57; 95%CI 2.09-6.10, p<.001) remained significant after controlling for symptom levels at baseline.

Figure 1. The effect of type-D personality on (A) symptoms of fatigue and (B) symptoms of depression at 12-month follow-up stratified by IHD stage

(A)



B)



DISCUSSION

The prevalence of symptoms of fatigue and depression in IHD is well documented [19-22]. Increased levels of fatigue and/or depression have been found in CAD [23-26], post-MI [2,3,6], and CHF patients [4,5,8], but to our knowledge there has been no systematic comparison between IHD stages and psychological symptom levels. Therefore, the primary aim of the current study was to examine the effect of IHD stage on fatigue and depressive symptoms at 12-month follow-up. Ischemic CHF-patients were used to reflect end-stage IHD, whereas PCI patients were used to reflect early-stage IHD. We found that IHD stage predicted neither symptoms of fatigue nor symptoms of depression. This may seem counter-intuitive, since CHF patients generally have poorer prognosis as compared to CAD patients [27], and one may expect this to be accompanied by increased psychological symptom burden. However, the physiological course of a disease may not be on par with the psychological course. Earlier studies have described adaptive psychological mechanisms in chronic illnesses [28,29], which may serve as an explanation for the current findings. On average, CHF patients have a longer and more severe cardiac history as compared to CAD patients. Therefore, they may be better accustomed to the disease, which in turn could mask the objectively increased physical deterioration.

Previous research has shown that type-D personality is associated with symptoms of fatigue and depression in patients with CAD [9,10]. This was also confirmed in the current study. In addition, we found that the effect of type-D personality on symptoms of fatigue and depression was the same for CHF and CAD patients, and that this effect was independent of other demographic and clinical risk factors.

The present findings hold some important implications. First, clinically manifest symptoms of fatigue and depression were equally prevalent in CHF and CAD patients despite a marked difference in IHD stage. This suggests that clinicians should be cautious when attributing self-reported symptoms to the disease itself, with psychological factors likely playing an important role. We found that type-D personality rather than IHD stage was associated with symptoms of fatigue and depression. The findings of the current study and other studies [30-32] indicate that a personality approach may be

advantageous in terms of identifying patients at high risk for increased psychological symptomatology. It is important to emphasize that this should not be limited to type-D personality, fatigue, and depression, but that we should focus on a broader spectrum of behavioral and psychological factors [33]. Therefore, future studies are warranted that give a more in-depth insight into the differences in psychological make-up of patients at different stages of CAD. To optimize risk stratification in clinical practice, future studies should also focus on identifying symptoms that are most cardio-toxic in terms of predicting clinical outcome, in line with a previous study in which we showed that hopelessness was the most cardio-toxic depressive symptom [34].

This study had a number of limitations. First, we only focused on symptoms of fatigue and depression. Other psychological factors might be important as well, such as anxiety [33,35]. Second, our results may not be generalizable to other cardiac patient groups, for example CABG or post-MI patients. Third, retrospective bias may have influenced the measurement of symptoms of fatigue and depression since patients were asked to report distress levels in the period preceding the administration. Fourth, we did not have information on educational level and co-morbid medical illness. Strengths of the current study were its prospective design and the use of validated and reliable psychological measures.

In conclusion, type-D personality but not IHD stage predicted symptoms of fatigue and depression at 12-month follow-up. In addition, IHD stage did not moderate the effect of type-D on symptom levels. Careful consideration of patients' self-reported symptoms is therefore warranted. CAD research and clinical practice may benefit by adopting a personality approach in order to explain individual differences in symptom presentation and to identify patients at high-risk of adverse health outcomes.

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CHAPTER 4:

Vital exhaustion and cardiovascular prognosis in myocardial infarction and heart failure: Predictive power of different trajectories

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Submitted for publication

ABSTRACT

Aim: We examined the different trajectories of vital exhaustion (VE) over a 12-month period and their impact on prognosis in a sample of myocardial infarction (MI) and chronic heart failure (CHF) patients. **Methods:** Consecutive MI (N=407) and CHF patients (N=297) were assessed at baseline, 3- and, 12-month follow-up for symptoms of VE. Latent growth mixture modelling was used to examine the course of VE over time. The combined clinical endpoint was defined as cardiac hospital readmission or death. **Results:** Four distinct trajectories for VE were found: low VE, decreasing VE, increasing VE, and severe VE. Sex, marital status, left ventricular ejection fraction, psychotropic medication, sample group (CHF vs. MI), and depressive symptoms were associated with VE, varying according to classes. The mean follow-up period was 25.3 months in which 34.7% of the patients experienced an event. Multivariate Cox regression showed that patients in the increasing VE class (HR=1.16; 95%CI 1.58-3.61, p=.01), and the severe VE class (HR=1.69; 95%CI 1.31-2.64, p=.02) had an increased risk for adverse cardiovascular events as compared to low VE class. Decreasing VE was not related to prognosis (HR=.97; 95%CI .66-1.69, p=.81). **Conclusions:** VE trajectories varied across cardiac patients, and had a differential effect on cardiovascular outcome. Increasing VE, and severe VE classes were predictors of poor prognosis. These results suggest that identification of cardiac patients with an increased risk of adverse health outcomes should be based on multiple assessments of VE.

INTRODUCTION

Vital exhaustion (VE) is a frequently observed phenomenon in patients with coronary artery disease and chronic heart failure (CHF) (1-3). The most commonly used definition of VE is that of unusual tiredness, increased irritability, and feelings of demoralization (4). VE has been associated with a 2 to 3 fold increased risk of mortality and morbidity in patients with coronary artery disease (2,3,5), and several potential biological pathways have been identified to explain this association. VE has been shown to relate to increased lipid metabolism (6), hypocortisolemia (7,8), reduced fibrinolytic capacity (9,10), parasympathetic withdrawal (11), and increased levels of cytokines, e.g. IL-6 (12,13).

The 21-item Maastricht Questionnaire (MQ) is often used to assess VE (4). Previous studies have shown that VE as measured by the MQ is not similar to symptoms of fatigue, but additionally comprises factors such as depressive symptoms, sleep problems, and lack of concentration (3,14-16). It has been shown that VE is prevalent in both patients with myocardial infarction (MI) and CHF patients (3,17), but it is not clear whether levels of VE differ across these patient groups. Given disease stage, VE might also be differently related to cardiovascular prognosis.

Although previous studies have stressed the importance of VE in cardiac disease (3,18-20), there is a paucity of research on the evolution and/or persistence of VE. Patients may have varying courses of VE and, hence, potentially differential risks of adverse health outcomes. Knowledge of VE trajectories, their clinical and psychological characteristics, and their prognostic impact might allow for the identification of high-risk cardiac patients who may need additional clinical care above and beyond the standard medical management of the disease.

Since the course of VE has not been studied in cardiac patients, the current study's objective was to examine 1) the course and characteristics of VE during a 12-month period, and 2) their impact on cardiovascular prognosis in a combined sample of MI and CHF patients.

METHODS

Patients

In order to cover both acute and chronic cardiac disease, we combined two different samples. A sample of patients who recently had a myocardial infarction (MI) was included to reflect acute cardiac disease, whereas a sample of patients suffering from chronic heart failure (CHF) was included to reflect chronic cardiac disease. This resulted in a total sample of 704 patients. The MI patients comprised 407 patients that participated in the DepreMI study (21), which is a naturalistic follow-up study of the impact of depressive symptoms on cardiac prognosis in MI patients in four hospitals in the North of The Netherlands. Patients admitted for an MI between September 1997 and September 2000 were included and followed until April 2002. Patients received usual aftercare for their MI and depressive symptoms. Of the 528 patients that were initially included, 60 patients were lost during follow-up (i.e. refusal, death), and 61 patients had missing questionnaire data on 2 or more measurement points, leaving 407 patients for the present study. Inclusion criteria were a) chest pain for at least 20 minutes, b) creatinine phosphokinase levels 100% above normal or creatinine phosphokinase MB levels above 10%, and c) presence of new pathological Q waves on the electrocardiogram in at least two leads. Exclusion criteria were life expectancy of less than a year (because of noncardiac condition), too poor physical condition according to hospital staff, cognitive dysfunction, inability to speak or read Dutch, occurrence of an MI in patients admitted for another reason, and follow-up visits scheduled in a nonparticipating hospital.

The CHF patients comprised 297 consecutive patients with systolic heart failure and a left ventricular ejection fraction (LVEF) ≤40%, visiting the heart failure outpatient clinic of the TweeSteden hospital, Tilburg, the Netherlands. Of the 378 patients that were initially included, 44 patients died during the first year of the study, and 37 patients had missing questionnaire data on 2 or more measurement occasions, leaving 297 patients for the present study. Patients with diastolic heart failure, age ≥80 years, myocardial infarction in the month prior to inclusion, other life-threatening diseases, and no or insufficient understanding of spoken and written Dutch language were excluded beforehand.

Patients completed a questionnaire at baseline, 3-month follow-up, and 12-month follow-up. The study protocol was approved by the institutional review boards of the participating hospitals, and was conducted conform to the Helsinki Declaration. Every patient provided written informed consent.

Vital exhaustion

VE was assessed by the 21-item Maastricht Questionnaire (4). Each item is originally rated according to a three-point scale (*Yes*=0; *?*=1; *No*=2), and a total score was calculated by summing the answers. The reliability of the total scale is good with Cronbach's alpha of 0.89 (5). Frequency analysis on every single item revealed that the question mark category was rarely used (<10%). Therefore, we decided to divide the total scores by a factor 2 and to round up to integers at a zero point five level. Hereby, we considered these scores as count variables of the number of VE symptoms. From a psychometric perspective, this is more appropriate than using the scores as a continuous variable.

Symptoms of depression

Symptoms of depression were measured by means of the Beck Depression Inventory (BDI) (22). Each item is rated on a 0-3 scale. A total score is obtained by summing together all the items. The BDI is a reliable and well-validated measure of depressive symptomatology (23), and is the most widely used self-report measure of depression. This subscale was dichotomized using the standardized BDI cut-off score of ≥10 versus BDI scores <10.

Demographic and clinical variables

Demographic variables included sex, age (<60 yrs vs. ≥60 yrs), and marital status (partner vs. no partner). Clinical variables comprised smoking status, LVEF (<40% vs. ≥40%), previous MI, diabetes mellitus, and cardiac medication. Information on clinical variables was obtained from the medical records and from the treating cardiologist or heart failure nurse.

Cardiovascular prognosis

The combined clinical endpoint was defined as cardiovascular hospital readmission or cardiovascular death. Information on potential end points was collected from hospital records and the patient's primary care physician. Mean follow-up duration was 25.4 months (SD=13.3).

Statistical analyses

Latent class analysis (LCA) was employed to examine trajectories of VE symptoms in cardiac patients over a 12-month period (24). A latent growth Poisson mixture model was fitted to identify classes of individuals following similar patterns of behavior over time. The model assumes unobserved latent variables to explain the associations among observed scores, and can be seen as a categorical equivalent of factor analysis. One of the problems with fitting these types of latent class models is that the categorization into classes is dominated by the overall symptom levels making it less likely that the model picks up symptom changes. A way to overcome this problem is the inclusion of a random intercept (25).

To determine the optimal number of trajectories, the Aiken Information Criterion 3 (AIC3) was used, with a lower AIC3 indicating a better fit. However, a difference of less than 3 will favor the least complex model. Recent studies have shown that AIC3 is a better criterion than BIC and AIC in determining the number of latent classes in LC models (26,27).

For comparison between classes we used the Chi-square test for discrete variables. Adjusted Standardized Residuals (ASRs) were used to identify groups responsible for significant differences. A residual greater than 2.0 was taken to indicate a significantly higher frequency, and a residual less than -2.0 was considered to indicate a significantly lower frequency, than expected if the independence hypothesis was true (28).

Multivariate Cox proportional hazards regression was used to assess whether VE trajectories predicted the combined end-point of cardiovascular readmission or death. In the regression model, we included age, gender, marital status, smoking status, diabetes mellitus, previous MI, disease severity (LVEF), beta blockers, calcium antagonists, aspirin, psychotropics, and depressive symptoms because of their relation with cardiovascular prognosis

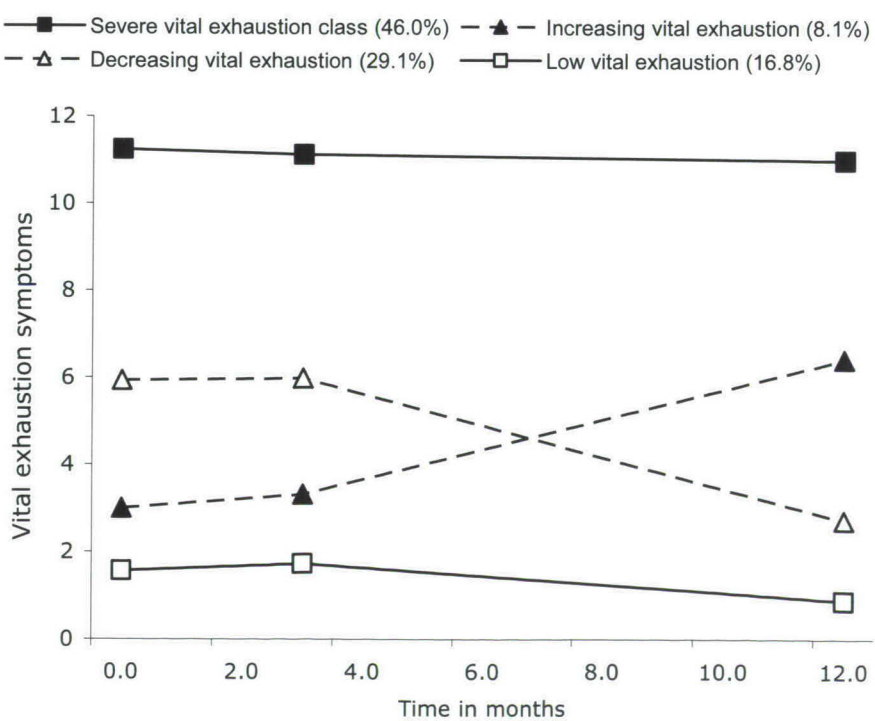
(29-36). The LCA was performed with the program Latent GOLD 4.5 (24). All other data were analyzed using SPSS 15.0.1 for Windows. A similar approach has previously been used in MI- (37), PCI- (38), and PAD patients (39).

RESULTS

Trajectories of vital exhaustion

Figure 1 displays the four distinct developmental trajectories for vital exhaustion. The AIC3 improved from one class of VE (AIC3 = 11526) to four classes of VE (AIC3 = 11315), whereas a relative decline was observed in the five class model (AIC3 = 11322). Compared to the three class model (AIC3 = 11323), the four class model achieved a significant improvement in fit. The four class model was therefore adopted for further analysis.

Figure 1. Observed trajectories of vital exhaustion



The first class (16.8% of the sample) was classified as the low VE group (intercept=0.57, $p<.001$; slope= -0.06, $p<.001$), and had low levels of VE on all time points. The first class was used as a reference category. The second class (29.1%) was characterized by a decrease in VE symptoms over time (intercept=1.81 , $p<.001$; slope= -0.06, $p<.001$). The third class (8.1%) was described as increasing VE (intercept=1.30, $p<.001$; slope= 0.03, $p=.09$). Finally, the fourth class (46.0%) was classified as severe VE (intercept=2.38, $p<.001$; slope= -0.0023, $p=.34$) with high levels of VE on all time points.

Characteristics of vital exhaustion trajectories

There were a number of differences in demographic, clinical, and psychological characteristics at baseline as a function of VE class (Table 1).

Table 1. Baseline characteristics stratified by vital exhaustion class*

Variable	Total	Low vital exhaustion	Decreasing vital exhaustion	Increasing vital exhaustion	Severe vital exhaustion	*p*-value
	% (n)	(n=118)	(n=205)	(n=57)	(n=324)	
Male sex	76.6 (539)	**87.3 (103)**	79.0 (162)	**93.0 (53)**	**68.2 (221)**	<.001
Age≥60	62.9 (443)	55.1 (65)	67.3 (138)	61.4 (35)	63.3 (205)	.18
No partner	19.2 (135)	**11.0 (13)**	18.0 (37)	12.3 (7)	**24.1 (78)**	.007
Smoking	38.2 (269)	40.7 (52)	32.7 (66)	50.9 (29)	38.9 (126)	.06
Previous MI	29.8 (210)	21.2 (25)	31.2 (64)	22.8 (13)	33.3 (108)	.05
Diabetes	15.2 (107)	11.9 (14)	16.1 (33)	5.3 (3)	17.6 (57)	.07
Heart failure†	42.2 (297)	37.3 (44)	39.5 (81)	**26.3 (15)**	**48.5 (157)**	.005
LVEF<40%	56.0 (394)	50.0 (59)	54.1 (111)	45.6 (26)	**61.1 (198)**	.05
Beta blocker	72.5 (510)	78.8 (93)	69.8 (143)	75.4 (43)	71.5 (231)	.32
Calcium Ant.	17.5 (123)	19.5 (23)	16.6 (34)	19.3 (11)	17.0 (55)	.89
Aspirin	67.3 (474)	66.1 (78)	69.3 (142)	75.4 (43)	65.1 (211)	.42
Psychotropics	8.1 (57)	**1.7 (2)**	4.4 (9)	1.8 (1)	**6.4 (45)**	<.001
Depr. Sympt.	27.6 (194)	**3.4 (4)**	**9.3 (19)**	**5.3 (3)**	**51.9 (168)**	<.001

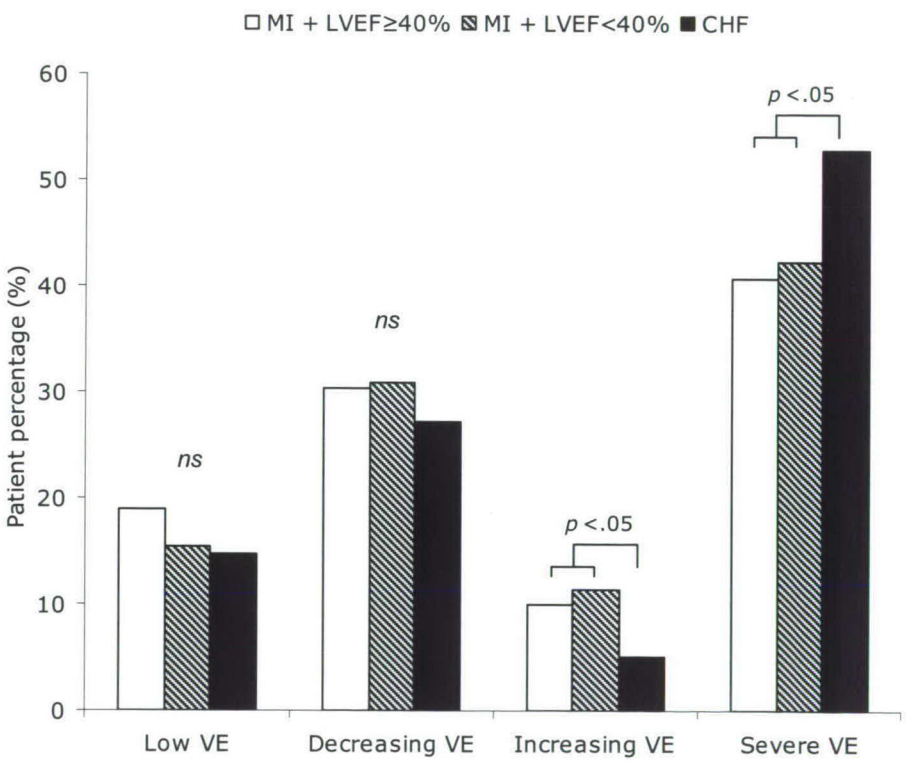
* Numbers in bold represent an absolute adjusted standardized residual > 2.0

† CHF group as compared to the MI group

Departure from independence was most pronounced in the extreme VE groups, (Table 1; numbers in bold). Patients in the low VE group were more likely to be male (ASR=3.0), and to have a partner (ASR= -2.5). In addition, they were less likely to be on psychotropics (ASR= -2.8), and to be depressed (ASR= -6.4). Patients in the decreasing VE group were less likely to be depressed (ASR= -7.0). Other deviations were not observed in this class. Patients in the increasing VE group were more likely to be male (ASR= 3.1), and MI patient

(Figure 2). Furthermore, these patients were less likely to be depressed (ASR= -3.9). Finally, patients in the severe VE group were more likely to be female (ASR= -4.8), alone (ASR=3.0), on psychotropic medication (ASR=5.2), depressed (ASR= 13.3), and to have decreased LVEF (ASR=2.5). As displayed in figure 2, CHF patients were more likely to be in the severe VE group as compared to MI patients (ASR=3.1), independent of LVEF.

Figure 2. Percentage of patients per VE class stratified by sample group & LVEF



Trajectories of vital exhaustion and cardiovascular prognosis

The mean follow-up period was 25.4 months (SD=13.3). During this period, 244 patients (34.7%) experienced an adverse cardiovascular event. Lower LVEF was associated with an increased risk for adverse cardiovascular events (Table 2). Previous MI showed a trend towards significance.

Univariate Cox regression analysis revealed that the event rate in the increasing VE class, and the severe VE class was significantly higher as compared to the low VE class (Figure 3). In multivariate analysis, increasing VE and severe VE remained significant predictors of adverse cardiovascular events (Table 2). Compared to the low VE group, patients in the increasing VE class (HR=1.16; 95%CI 1.58-3.61, p=.01), and in the severe VE class (HR=1.69; 95%CI 1.31-2.64, p=.02) had an increased risk for cardiovascular events. Patients in the decreasing VE class had a similar risk for cardiovascular events (HR=.97; 95%CI .66-1.69, p=.81) as compared to the low VE class. Adding sample group (MI vs. CHF) as a predictor did not significantly alter the results presented in Table 2.

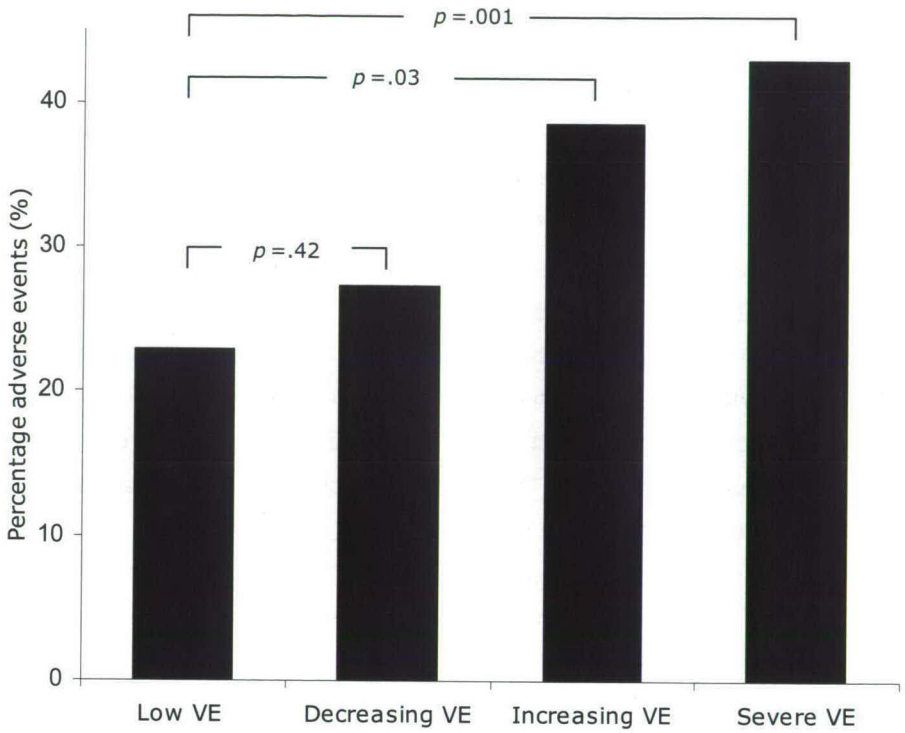
Table 2. Trajectories of vital exhaustion and cardiac prognosis (multivariate)

Variable	HR	95%CI	*p*-value
Male sex	.97	.71-1.32	.82
Age≥60	1.16	.86-1.58	.33
Having no partner	.95	.69-1.31	.76
Smoking	1.08	.81-1.43	.61
Previous MI	1.32	.99-1.75	.06
Diabetes	1.28	.93-1.77	.14
LVEF<40%	**1.94**	**1.36-2.75**	**<.001**
Beta blocker	.80	.60-1.06	.13
Calcium antagonists	.81	.56-1.18	.27
Aspirin	.84	.63-1.11	.21
Psychotropic medication	1.26	.84-1.91	.27
Depressive symptoms	1.13	.82-1.54	.45
Decreasing vital exhaustion	1.06	.66-1.69	.81
Increasing vital exhaustion	**2.04**	**1.15-3.61**	**.01**
Severe vital exhaustion	**1.69**	**1.08-2.64**	**.02**

DISCUSSION

To our knowledge, this is the first study to examine the course of vital exhaustion in a combined sample of MI and CHF patients. We found four distinct trajectories for VE: (i) low levels of VE on all time points; (ii) decreasing levels of VE over time; (iii) increasing levels of VE over time; (iv) high levels of VE on all time points. Sex, marital status, LVEF, psychotropic medication, sample group (CHF vs. MI), and depressive symptoms were

Figure 3. Cardiovascular event rate stratified by VE class (univariate)



associated with VE, varying according to classes. Multivariate Cox regression showed that patients in the increasing VE class and the severe VE class had an increased risk for adverse cardiovascular events as compared to low VE class. Patients in the decreasing VE class had a similar risk for cardiovascular events as compared to the reference category.

The results of the present study advocate the use of latent growth mixture modeling to study the course of symptom levels over time which has also been argued in other studies (21,37-39). Similar to our study, these investigations have also found support for multiple rather than one trajectory, although they studied depression (21,37,39) and anxiety (38). Our approach was however a bit different from the previous studies because 1) we allowed the error terms to vary between classes which was not the case in the study of

Kaptein et al. (21), and 2) we included a random intercept to remove the overall response level effects (25). In our opinion, both adjustments improved the model specification considerably, as was demonstrated by higher AIC3 values (not reported) in VE models with fixed error terms and without a random intercept.

The most important finding is that two trajectories of VE were associated with an increased risk of cardiovascular events, representing chronic severely exhausted patients and patients in which levels of VE increased during the follow up year. Of interest, MI patients were relatively more present in the increasing VE class as compared to CHF patients. Our findings thus suggest that a significant number of patients after a MI do not fully recover but deteriorate over time, which in the current study is expressed as an increase in the number of VE symptoms and subsequently an increased cardiac risk. Patients in this class might reflect a group of patients that do not respond to standard treatment procedures. These findings appear to be consistent with previous observations by Carney (40), De Jonge (41) and Kaptein (21) who found that persistence of depressive symptoms (despite treatment) was associated with an increased cardiac risk. Of note, in those studies depression was assessed with the BDI, in which somatic symptoms of depression (such as fatigue and sleeping difficulties) are relatively overrepresented. In contrast, CHF patients were relatively more present in the severe VE class. CHF patients on average have a longer and more severe cardiac history and did not experience a recent acute coronary syndrome. CHF patients may therefore display a more stable pattern of vital exhaustion over time. As a consequence, the most vulnerable class of CHF patients is characterized by a chronic, severe level of VE. Thus, the most vulnerable MI and CHF patients may differ in their patterns of VE.

From a clinical point of view, knowledge about factors characterizing trajectories that display changes over time is important as they point to targets for intervention. Importantly, the findings of the present study indicate that VE trajectories are differently related to an increase of adverse cardiovascular events. In a previous study, we have shown that symptom profiles of vital exhaustion in CHF patients, measured at a single time point, were associated with rehospitalization (3). It would be interesting to study these symptom

profiles using a latent growth mixture modeling approach, and examine the effect of symptom profile trajectories on cardiovascular prognosis. Furthermore, in the multivariate Cox model, we controlled for depressive symptoms measured at baseline, and demonstrated that trajectories of VE independently predicted our outcome measure. The potential effects of depressive symptoms at later time points were ignored. It would be worthwhile to investigate the distinctiveness of VE and depression using a joint trajectory modeling approach (42) providing full control of each others effects on outcome measures. Generally, large-scale studies should give a more in-depth insight into the differential effect of the VE trajectories on cardiovascular prognosis.

This study has a number of limitations. First, the cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern might have influenced patient selection. Second, the examined predictors of the VE trajectories were only assessed once. Given that, for example, depressive symptoms were identified as an independent predictor of persistent VE, it is possible that these levels may be attributed to persistent depressive symptoms, rather than baseline levels. Nevertheless, the strengths of the current study were the repeated assessment of VE over time, the prospective design examining the course of VE over time using a state-of-the-art modeling approach, and the use of a semi-objective medical outcome. Finally, we used a reliable and valid measure of vital exhaustion.

In summary, we found four distinct trajectories for vital exhaustion. Several predictors, varying according to classes, could be identified with sex, marital status, LVEF, psychotropic medication, sample group (CHF vs. MI), and depressive symptoms being the most prominent ones. Increasing VE class, and the severe VE class had an increased risk for adverse cardiovascular events as compared to low VE class. Patients in the decreasing VE class did not have an increased risk for adverse events as compared to the reference category.

Future studies are warranted to confirm these findings, given that this was the first study to examine the course of VE in cardiac patients. The results of the present study may help identify distinct groups of patients with potentially differential risks of adverse health outcomes, guide future interventions, and therefore be valuable for both research and clinical practice.

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CHAPTER 5:

Symptoms of Fatigue in Chronic Heart Failure Patients: Clinical and Psychological Predictors

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ABSTRACT

Objective: To examine the role of clinical and psychological characteristics as predictors of fatigue in CHF. **Background:** Little is known about predictors of fatigue in CHF. Next to heart failure characteristics, depressive symptoms and type-D personality may explain individual differences in fatigue. **Methods:** At baseline, 136 CHF outpatients (age≤80) completed a questionnaire to assess depressive symptoms, type-D personality and cardiac symptoms. At one-year follow-up, they completed the Dutch Exertion Fatigue Scale and the Fatigue Assessment Scale to assess symptoms of fatigue. Medical information was obtained from the patients' medical records. **Results:** Exertion fatigue and general fatigue were identified as different manifestations of fatigue. We found that exertion fatigue at 12-month follow-up was predicted by decreased exercise capacity (β=-.35; p<.001), dyspnoea (β=.24; p=.002), hypertension (β=.16; p=.03), and depressive symptoms (β=.16; p=.05). In contrast, general fatigue at 12-month follow-up was predicted by dyspnoea (β=.24; p=.003), depressive symptoms (β=.27; p<.001), type-D personality (β=.17; p=.03), and sleep problems (β=.20; p=.01). Together, these variables explained 32 and 37 percent of the variance, respectively. **Conclusion:** The present study showed that fatigue was related to both clinical and psychological characteristics. The use of this knowledge may lead to a better understanding and treatment of the clinical manifestations of fatigue in CHF.

Introduction

Chronic heart failure (CHF) is accompanied by severe symptoms and poor prognosis. Recent studies have underlined the importance of symptoms in CHF, both in terms of prognosis [1,2] and quality of life [3]. One poorly understood symptom of CHF is fatigue.

Fatigue is often rated as one of the most disabling symptoms in chronic heart failure [4], however, little is known about its predictors [1,5,6]. One small study in women with CHF found that only symptoms of dyspnoea predicted fatigue [6]. Clearly, more studies are needed to give a more in-depth insight into the variables that predict fatigue. In addition, previous research has shown that different forms of fatigue are relevant to CHF patients; these are exercise related symptoms of fatigue, and general feelings of fatigue which are not necessarily related to exercise [7]. Accordingly, it is necessary to examine the dimensionality of fatigue before relating it to other variables.

Haemodynamically, symptoms of fatigue during exercise are thought to arise from failure of muscle perfusion due to an inadequate rise in cardiac output. However, many studies have shown that there is no relation between cardiac performance and exercise performance [8,9]. Recently, it has been suggested that chronic, low grade haemodynamic stress as seen in CHF, may lead to dominance of catabolic processes. This in turn leads to skeletal myopathy, causing the sensation of fatigue [10]. Future studies should aim to demonstrate to what extent skeletal myopathy is able to explain individual differences in fatigue.

Besides physiological explanations for symptoms of fatigue in CHF, psychological factors should also be taken into account. Depressive symptoms have previously been associated with fatigue in CHF [11,12]. However, the role of personality as a predictor of fatigue in CHF has received little attention up to now. A study in patients with ischaemic heart disease revealed that patients with a type-D personality, a joint tendency toward negative affectivity and social inhibition, were more likely to report symptoms of fatigue and exhaustion [13]. Comparable results were found in a related set of personality variables in patients with multiple sclerosis [14]. Therefore, it seems important to examine the role of personality as a predictor of fatigue in CHF patients as well.

The aim of the present prospective study was (1) to examine the nature of fatigue, and (2) to examine the role of clinical and psychological characteristics as predictors of fatigue in CHF.

Methods

Participants

The sample included 136 CHF patients visiting the heart failure outpatient clinic of the Twee Steden Ziekenhuis, Tilburg, the Netherlands. As displayed in Table 1, the majority of subjects was male, married, unemployed, non-smokers, and not academically educated. About half the sample was classified as NYHA-class III/IV, had a cardiac history, and ischaemic CHF. Only a minority of the sample were overweight and anaemic. Co-morbidities that were most common included hypertension, diabetes mellitus, and peripheral artery disease. Diuretics, ACE-inhibitors, and beta-blockers were the most prescribed medications.

Inclusion criteria were defined as systolic heart failure, LVEF $\leq$ 40%, and sufficient understanding of spoken and written Dutch language. Exclusion criteria were defined as diastolic heart failure, age $\geq$ 80 years, myocardial infarction in the month prior to inclusion, other life-threatening diseases, clinical signs of an acute infection, use of anti-inflammatory medication.

Patients filled out questionnaires with regard to personality, dyspnoea, and depressive symptoms at baseline, and fatigue at twelve-month follow-up. All patients participated voluntarily and signed informed consent. The study protocol was approved by the medical ethics committee of the St. Elisabeth Hospital, Tilburg, the Netherlands.

Symptoms of fatigue

Previous research has shown that general fatigue does not necessarily have a relationship with exertion [7]. Therefore, separate measures were used to assess exertion fatigue and general fatigue, respectively. Exertion fatigue may be defined as fatigue directly related to the performing of activities in daily living [7], whereas general fatigue has been defined as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work [15].

Table 1. Baseline characteristics

Age: Mean (SD)	65.6 (8.5)
Male gender	104 (76.5%)
Having a partner	106 (77.9%)
No academic education	117 (86.0%)
Unemployed	113 (83.1%)
NYHA-class III/IV	73 (53.7%)
LVEF: Mean (SD)	30.0% (6.9)
Ischemic aetiology	72 (52.9%)
Cardiac history*	76 (55.9%)
Non-smokers	102 (75.0%)
Co-morbidities	
Stroke	13 (9.6%)
COPD	13 (9.6%)
Renal insufficiency	17 (12.5%)
Liver disease	6 (4.4%)
Diabetes mellitus	34 (25%)
Hypertension	49 (36.0%)
Peripheral arterial disease	21 (15.4%)
Medication	
ACE-inhibitor	108 (79.4%)
All-antagonist	22 (16.2%)
Diuretics	109 (80.1%)
Spironolacton	29 (21.3%)
Digoxin	43 (31.6%)
Beta blocker	91 (66.9%)
Statins	67 (49.3)
Aspirin	63 (46.3%)
Anaemia (Hb≤120 g/L)	27 (19.9%)
BMI: Mean (SD)	28.3 (4.9)

BMI: body mass index; LVEF: left ventricular ejection fraction.

* MI, angina, PCI, or CABG.

The Dutch Exertion Fatigue Scale (DEFS) assesses exertion fatigue by means of 9 items [10]. Items are answered with five response alternatives ranging from 0 (no) to 4 (yes). Chronbach's alpha is high (α=.91). The Fatigue Assessment Scale (FAS) was used to assess symptoms of general fatigue [16]. This questionnaire consists of 10 items, which are answered on a 5-point Likert scale, ranging from 1 (never) to 5 (always). The reliability of this instrument is high (α=.90).

Dyspnoea, chest pain, & sleep problems

Cardiac symptoms were measured by means of the 12-item Somatic complaints subscale of the Health Complaints Scale (HCS) [17]. Items are answered on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely). The items measuring chest pain, shortness of breath, and sleep

problems were used as separate subscales. The items measuring fatigue were excluded.

Symptoms of depression

Symptoms of depression were measured by means of the Beck Depression Inventory (BDI) [18]. Each item is rated on a 0-3 scale. The BDI is a reliable and well-validated measure of depressive symptomatology [19,20], and is the most widely used self-report measure of depression. Since the somatic items of the BDI may be confounded by symptoms of fatigue, only the cognitive-affective subscale was used [21]. Because of non-normality, the subscale was dichotomized at the highest tertile.

Type-D personality

Type-D personality was measured by means of the DS14 [22]. This 14-item questionnaire comprises two subscales, Negative Affectivity and Social Inhibition, each consisting of 7 items. The items are answered on a 5-point Likert scale, ranging from 0 (false) to 4 (true). Negative affectivity refers to the tendency to experience negative emotions across time/situations, whereas social inhibition refers to the tendency to inhibit the expression of emotions/behaviours in social interactions to avoid disapproval by others. Previous studies in coronary patients have shown that type-D's are at risk for a wide range of adverse health outcomes, including mortality [23], morbidity [24], and mood status [25].

A standardized cut-off score of ≥10 on both subscales classifies subjects as a type-D personality [22]. Initially, this cut-off corresponded to a median split of both subscales which resulted in a prevalence rate between 27 and 31 percent of type-D's among patients with coronary heart disease. In the present study, the prevalence rate of type-D was 26%, which is in accordance with the rates mentioned above. Both scales have good internal validity (α=.88 for Negative Affectivity and α=.86 for Social Inhibition).

In a sample of coronary patients who underwent cardiac rehabilitation, both negative affectivity and social inhibition were relatively stable over a 3 month period (test-retest r=.82 for Negative Affectivity and r=.72 for Social Inhibition), and DS14 mean scores did not change significantly over time. In

contrast, measures of mood and health status did show significant changes over this 3 month period [22], suggesting that a patients' score on the DS14 is relatively independent from changes in mood and health status.

Additionally, it has been shown that type-D is different from established personality constructs like neuroticism and extraversion, even though they are related. Negative affectivity only shared 46% of its variance with neuroticism, and social inhibition only shared 35% of its variance with extraversion [22]. Although more research on its situational stability is needed, the findings support the validity of type-D as a personality construct.

Demographics and clinical variables

Demographics included sex, age, educational level, marital status, and employment status. Medical variables, obtained from patients' medical record included Left Ventricular Ejection Fraction (LVEF), functional class (NYHA-classification), aetiology of heart failure, co-morbidities, cardiac history, and prescribed medications. Exercise capacity was measured by means of the six-minute walking test (walking small circuits of 52 meters), which was carried out within the hospital as part of this study. Patients were instructed to walk at a normal pace, and to continue walking until they were told to stop or until they experienced too many adverse symptoms. Patients were not encouraged to walk as far as possible because the test was meant to reflect daily life exercise capacity.

Statistical Analyses

Principal component analysis (PCA) with oblimin rotation was used to determine whether general fatigue and exertion fatigue could be distinguished from each other. Factors with an eigenvalue > 1 were retained according to Kaiser's criterion. KMO and Bartlett's test of sphericity were used as fit indices.

Prior to further statistical analyses, educational level, marital status, employment status, NYHA-class, aetiology of heart failure, co-morbidities, haemoglobin levels, and cardiac history were recoded into dichotomous variables.

Associations with fatigue at 12-month follow-up were examined with Pearson's product moment correlation coefficients for continuous variables, and with

point-biserial correlations for discrete variables. Factors that were significantly associated with fatigue at 12-month follow-up were entered into a stepwise regression procedure. Regression analyses were performed for each dimension of fatigue. In order to examine the generalizability of the models obtained by the stepwise procedure, the population cross-validation coefficient R_c^2 was computed using Steins formula [26]. It has been shown that the R_c^2 is a far more accurate correction for shrinkage than the adjusted R^2. In addition, R_c^2 is also preferred over empirical cross-validation [27,28].

RESULTS

Nature of fatigue

Principal component analysis on the two fatigue scales at 12-month follow-up revealed a 3-factor solution (Table 2). KMO (0.89) and Bartlett's test of sphericity (χ^2 (171, N=136) = 1580.2, $p<.001$) indicated that PCA was adequate for this data. Two specific components were found, i.e. exertion fatigue and general fatigue. The nonspecific third factor was excluded from further analysis. Items with component loadings >.40 and Δcross-loadings <.20 were used to construct subscales. Accordingly, 7-item subscales of exertion fatigue (α=.89) and general fatigue (α=.90) were formed, respectively. Exertion fatigue and general fatigue were moderately correlated (r=.55; $p<.001$).

Predictors of fatigue

Significant univariate correlates of exertion fatigue and general fatigue at 12-month follow-up are displayed in Table 3. Variables with a bivariate correlation ≥.30 with respect to exertion fatigue were exercise capacity, NYHA-class, dyspnoea, cardiac pain, and depressive symptoms. A correlation ≥.30 with general fatigue was found for sleep problems, dyspnoea, cardiac pain, depressive symptoms, and type-D personality.

Stepwise regression analysis revealed that exertion fatigue at 12-month follow-up was best predicted by exercise capacity, dyspnoea, hypertension, and depressive symptoms. Together, these four variables explained 32 percent of the variance in exertion fatigue. General fatigue at 12-month follow-up was best predicted by dyspnoea, depressive symptoms, type-

Table 2. Dimensions of fatigue at 12-month follow-up

Item	Content	F1	F2	F3
DEFS 9	It is fatiguing for me to go to a birthday party	.89		
DEFS 7	It is fatiguing for me to hoover	.89		
DEFS 8	It is fatiguing for me to visit someone	.85		
DEFS 6	It is fatiguing for me to clean up my household waste	.81		
DEFS 5	It is fatiguing for me to shop	.72		
DEFS 3	It is fatiguing for me to take a shower standing	.65		
DEFS 1	It is fatiguing for me to walk 10 minutes	.60		
*DEFS 2**	*It is fatiguing for me to walk 30 minutes*	*.50*	*-.35*	
*DEFS 4**	*It is fatiguing for me to go up- and downstairs*	*.46*	*-.35*	
FAS 6	I have problems starting things		-.83	
FAS 5	Physically, I feel exhausted		-.80	
FAS 8	I feel no desire to do anything		-.79	
FAS 3	I don't do much during the day		-.73	
FAS 1	I am bothered by fatigue	.30	-.67	
FAS 9	Mentally, I feel exhausted		-.66	-.46
FAS 2	I get tired very quickly	.33	-.62	
*FAS 4**	*I have enough energy for everyday life*		*-.33*	
*FAS 10**	*When I am doing something, I can concentrate quite well*			*.83*
*FAS 7**	*I have problems thinking clearly*		*-.54*	*-.56*

DEFS: Dutch Exertion Fatigue Scale; FAS: Fatigue Assessment Scale.

*Excluded from further analyses.

D personality, and sleep problems. Together, these four variables explained 37 percent of the variance in general fatigue (see also Table 4).

As displayed in Table 5, the amount of shrinkage was relatively small. This indicates that if the prediction equations were applied to other samples of chronic heart failure patients, then on average the same proportion of variance accounted for would be found. That is, the identified predictors of fatigue are likely to be valid in CHF patients.

DISCUSSION

Fatigue is one of the most prevalent and aggravating symptoms in CHF, and patients often rate fatigue as one of the most burdening consequences of CHF [4]. However, little is known about factors that explain individual differences in symptoms of fatigue [1,5,6]. Therefore, the primary aim of this prospective study was to identify predictors of fatigue in chronic heart failure patients. Exertion fatigue and general fatigue were identified as different manifestations of fatigue. We found that exertion fatigue at 12-month follow-up was predicted by decreased exercise capacity, dyspnoea, hypertension, and

Table 3. Univariate correlates of 12-month fatigue

Factor	12-month follow-up	
	r	*p*
Exertion fatigue		
Female sex	.23	.007
Low educational level	.24	.006
Unemployment	.23	.006
Exercise capacity	-.44	<.001
NHYA class III/IV	.30	<.001
Cardiac history	.17	.04
Stroke	.21	.013
Hypertension	.23	.008
Beta blocker	-.18	.04
Sleep problems	.29	.001
Dyspnoea	.33	<.001
Cardiac pain	.42	<.001
Depressive symptoms	.33	<.001
Type-D	.20	.02
General fatigue		
Exercise capacity	-.24	.005
NHYA class III/IV	.26	.002
COPD	.20	.02
Hypertension	.17	.05
Sleep problems	.42	<.001
Dyspnoea	.45	<.001
Cardiac pain	.44	<.001
Depressive symptoms	.42	<.001
Type-D	.36	<.001

Table 4. Determinants of 12-month fatigue in stepwise regression analyses

Factor	β	t-value	*p*-value
Exertion fatigue			
Exercise capacity	-.35	-4.62	<.001
Hypertension	.16	2.19	.03
Dyspnoea	.24	3.16	.002
Depressive symptoms	.16	2.01	.05
Full model information: R^2=.32; F (4,131)=15.18; *p*<.001			
General fatigue			
Sleep problems	.20	2.54	.01
Dyspnoea	.24	3.00	.003
Depressive symptoms	.27	3.67	<.001
Type-D	.17	2.23	.03
Full model information: R^2=.37; F (4,131)=19.22; *p*<.001			

Table 5. Cross-validity of regression models

Dependent variable	R^2	R_c^2	*Shrinkage (%)*
Exertion fatigue at follow-up	.32	.27	14.9
General fatigue at follow-up	.37	.33	11.9

depressive symptoms. In contrast, general fatigue at 12-month follow-up was predicted by dyspnoea, depressive symptoms, type-D personality, and sleep problems. The finding that exertion fatigue and general fatigue were not predicted by the same variables underlined that they represented different dimensions of fatigue.

In accordance with the study of Friedman et al. [6], feelings of fatigue were often accompanied by symptoms of dyspnoea. This was in line with expectations since dyspnoea and fatigue are core symptoms of CHF [29]. Depressive symptoms were also associated with symptoms of fatigue, which has previously been reported in studies of CHF [11,12], coronary [30], and stroke patients [31]. Apart from dyspnoea and depressive symptoms, exercise capacity and hypertension were important predictors of exertion fatigue. An intervention study by Mayou et al. [32] also found an association between fatigue and exercise capacity. Moreover, they found that increased exercise capacity after the intervention was associated with decreased fatigue. From previous studies, it is known that hypertension is often accompanied by fatigue, especially in combination with certain kinds of medication [33,34].

Next to dyspnoea and depressive symptoms, sleep problems and type-D personality emerged as predictors of general fatigue. Sleep problems and fatigue were found to be associated in previous studies in CHF [35] and cancer [36]. The effect of type-D on general fatigue might be explained by chronic exposure to distress. Over time, the chronic nature of type-D may elicit a discrepancy between resources and demands, which in turn may lead to greater feelings of general fatigue as compared to non-type-D's. Moreover, the association is in line with studies in coronary artery disease [13] and multiple sclerosis [14]. The study by Friedman et al. [6] did not find a relationship between fatigue and personality in CHF. However, they examined the effect of optimism and pessimism, instead of type-D personality. Although optimism/pessimism has been linked to negative affectivity [37], type-D

personality does not only comprise negative affectivity, but also social inhibition. This different finding could also be explained by the fact that the present study used different questionnaires to assess fatigue, and by the fact that the sample characteristics were not similar. Their subjects were more likely to be female, to be older, to be unmarried, and to have a better left ventricular ejection fraction as compared to our sample.

To our knowledge, this was the first study in *chronic* heart failure patients that tried to identify predictors of both exertion and general fatigue. Exertion fatigue was primarily predicted by physical characteristics, whereas general fatigue was predicted by both physical and psychological characteristics. This distinction might be important with respect to future interventions aimed at the reduction of fatigue in CHF patients. After all, it is unclear if and to what extent interventions should focus on either physical symptoms, psychological symptoms, or both. Future studies should also aim to reduce the effect of personality on general fatigue. Although changing personality characteristics is very difficult, previous research has shown that type-D's benefit from behavioural interventions in terms of mood and health status [22]. Hence, targets of counselling could be improvement of self-management abilities, consolidation of the social network, and improving coping abilities. The results of this study are important, because use of this knowledge by doctors and nurses may lead to a better understanding of the clinical manifestations of fatigue in CHF, which in turn may lead to a more effective treatment.

This study had a number of limitations. First, there may have been a bias in the selection of patients. The cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern might have influenced selection. Secondly, some variables were assessed by means of self-report.

In summary, the present study showed that fatigue was predicted by both clinical and psychological characteristics. Exertion fatigue at the 12-month follow-up was predicted by dyspnoea, exercise capacity, hypertension, and depressive symptoms, whereas general fatigue was predicted by dyspnoea, depressive symptoms, type-D personality, and sleep problems.

Although the present study revealed a number of predictors of fatigue in CHF, a large portion of variance remained unexplained. Therefore, future studies should focus on identifying these predictors. We suggest that more physiological measures, which are known to be abnormal in CHF patients and which are relevant with respect to symptoms of fatigue, for example measures of abnormal muscle metabolism and enhanced ergo reflex response, should be used [10]. Furthermore, future studies should examine the specific role of exertion fatigue and general fatigue as predictors of poor prognosis in CHF. Since some studies have already identified the importance of fatigue in terms of CHF prognosis [1,2], it is also necessary to identify potential mechanisms through which fatigue exerts its toxic effect. In this regard, it would be interesting to investigate whether fatigue is related to poor self-management. After all, it is well documented that poor self-management is associated with adverse clinical outcome [38].

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CHAPTER 6:

Fatigue levels in stroke patients as compared to end-stage heart failure patients: Application of the Fatigue Assessment Scale

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ABSTRACT

Objectives: The aim of the present study was to examine the assessment of fatigue by the Fatigue Assessment Scale (FAS) in stroke patients and to compare the levels of fatigue as reported by stroke patients, heart failure patients, and healthy controls. **Design:** Cross-sectional analysis. **Setting:** Stroke rehabilitation unit, heart failure outpatient clinic, general Dutch population. **Participants:** Three different samples were included: 80 stroke patients, 137 heart failure patients, and 160 healthy controls. **Measurements:** Fatigue was measured by means of the FAS at baseline and at 2-month follow-up. Depressive symptoms (BDI) were assessed at baseline. **Results:** The internal consistency (α) of the FAS was .77 both at baseline, and at 2-month follow-up. Test-retest reliability was .81 for a 2-month interval. Factor analysis of the combined pool of FAS and BDI items revealed two distinct factors that measure fatigue and depression as two separate constructs. Stroke patients (15.3 ± 7.6) and CHF patients (16.5 ± 7.9) reported similar levels of fatigue (p=.44). The level of fatigue in stroke and heart failure patients was considerably higher as compared to healthy controls (9.2 ± 5.6; p<.001). Using the healthy controls as a reference group, multivariable logistic regression revealed that stroke patients were at a 6-fold increased risk (OR=6.18;95%CI 3.31-11.55, p<.001), and heart failure patients were at an 8-fold increased risk (OR=8.03;95%CI 4.63-13.94, p<.001), for having fatigue symptoms. **Conclusion:** The FAS is an adequate measure of fatigue in stroke patients. Levels of fatigue in stroke patients are similar to levels found in heart failure patients, emphasizing its clinical significance in stroke.

INTRODUCTION

Symptoms of fatigue are common among stroke patients. A substantial proportion of stroke patients perceive fatigue as either their worst or one of their worst symptoms.(1) Previous studies have reported that the prevalence of post-stroke fatigue varies between 39-72%.(2) Nonetheless, fatigue has received little attention in the stroke literature(3-5), which may partially be due to its ambiguous nature.

A common way of assessing perceived fatigue is by means of questionnaires. A recent study evaluated different fatigue scales that have been used in stroke patients.(6) Based on their results, these authors recommended the Fatigue Assessment Scale(7) (FAS) to measure fatigue after stroke because the FAS had face validity, was feasible for most patients, had a good test-retest reliability, and had high construct validity. Although promising, these findings need to be replicated in a different sample of stroke patients.

The level of fatigue in stroke patients has previously been compared to healthy controls(1) and to patients with multiple sclerosis(8). Since stroke fundamentally is a vascular disease, it would be interesting to compare the levels of fatigue to cardiac patients as well. Within the spectrum of cardiovascular diseases, fatigue is most common in chronic heart failure(9) (CHF) which could therefore serve as a useful reference group to compare the levels of fatigue in stroke with.

The aim of the present study was 1) to examine the assessment of fatigue by the FAS in stroke patients, and 2) to compare the levels of fatigue as reported by stroke patients, CHF patients, and healthy controls.

METHODS

Participants

The first sample included 80 consecutive stroke patients visiting the stroke rehabilitation unit of nursing home 'De Hazelaar', Tilburg, the Netherlands. Their mean age was 74.1 years (± 6.6), 44 (55%) were male, and 38 (47.5%) had a low educational level (i.e. primary school). Forty-one (51.3%) had a right hemisphere stroke. Nineteen (23.7%) had a brainstem lesion, 26 (32.5%) had a subcortical lesion, and 22 (27.5%) had a cortical

lesion. No information on stroke location was available in 13 (16.3%) patients. The stroke sample was severely disabled. The average score on the physical dimension of the Stroke-Adapted Sickness Impact Profile (SA-SIP30)(10) was 72.8% (± 31.5) on the body care and movement subscale, 77.9% (± 26.0) on the mobility subscale, 82.1% (± 29.0) on the ambulation subscale, and 36.3% (± 30.6) on the alertness behavior subscale. Levels of disability were similar across stroke locations. The mean time between stroke and study inclusion was 7.6 months (± 5.4). Stroke patients that suffered from reduced level of consciousness, severe language deficits, multiple cognitive deficits reflecting dementia syndrome, or severe emotional problems were excluded. In addition, patients with other life-threatening diseases were excluded as well. Stroke patients were interviewed with regard to fatigue and depressive symptoms at baseline, and fatigue at 2-month follow-up.

The second sample comprised 137 end-stage CHF patients (NYHA-class III/IV) visiting the heart failure outpatient clinic of the TweeSteden Hospital, Tilburg, the Netherlands. Their mean age was 67.6 years (± 8.8), 98 (71.5%) were male, and 48 (35%) had a low educational level. The mean left ventricular ejection fraction was 28.9% (± 7.0). Inclusion criteria were systolic heart failure, LVEF ≤40%, and sufficient understanding of the spoken and written Dutch language. Patients with diastolic heart failure, age ≥80 years, myocardial infarction in the month prior to inclusion, other life-threatening diseases, or history of stroke were excluded. All patients completed a fatigue questionnaire at baseline.

Finally, a third sample of 160 healthy controls from the general Dutch population without a history of stroke or cardiovascular disease was used as a reference group. Their mean age was 69.3 years (± 6.0), 74 (46.3%) were male, and 34 (21.3%) had a low educational level. Research assistants were responsible for distributing the fatigue questionnaire. They approached the participants in person. Participants returned the questionnaires to the research assistants. Data were managed anonymously.

The study protocol was approved by the medical ethics committee of the respective institutions, and the study was conducted in accordance with the Helsinki Declaration. All participants provided written informed consent.

Measures

Symptoms of fatigue

Fatigue was measured by means of the FAS consisting of 10 items (e.g. "I am bothered by fatigue" or "I get tired very quickly"). The response scale is a 5-point scale (0=never to 4=always). Previous studies have shown that the psychometric properties of the FAS were good in samples of the general population(11), the working population(7), and the sarcoidosis population.(12) A recent study in 55 stroke patients revealed that the FAS had face validity, it was feasible for most patients, and it had good test-retest reliability and high construct validity, but low internal consistency.(6)

Depressive symptoms

The BDI was used to examine divergent validity of the FAS. Symptoms of depression were measured by using a shortened version of the Beck Depression Inventory (BDI) consisting of 13 items.(13) The item on suicide was excluded beforehand to limit the emotional burden. Each item is rated on a 0-3 scale. The BDI is a reliable and well-validated measure of depressive symptomatology that is also suitable for stroke patients.(14)

Disability

The Stroke-Adapted Sickness Impact Profile (SA-SIP30) was used to measure disability in the stroke sample.(10) Previous research has shown that SA-SIP30 provides more clinical information than other frequently used measures of disability.(15) Physical functioning was measured by the three subscales body care and movement, mobility, and ambulation. Level of cognitive impairment was measured by means of the alertness behavior subscale. Each item is rated on a dichotomous scale (Yes/No). Subscale scores are presented as a percentage of maximal dysfunction, ranging from 0% to 100%.

Statistical analyses

Cronbach's alpha coefficients were used to calculate the internal consistency. Test–retest reliability was established using a Pearson correlation between the FAS scores of the 80 patients who had completed the FAS twice.

Construct validity (divergent) was examined in two ways. First, a principal component analysis (PCA) with oblimin rotation was employed with the FAS and the BDI in order to examine the divergent validity of the FAS. Oblimin rotation was used because the extracted factors were expected to correlate.(12) The scree plot criterion was used to determine the number of factors. Secondly, Pearson correlations were calculated between the FAS scores and the scores on the BDI.

Analysis of variance (ANOVA) was used to compare levels of fatigue between stroke patients, CHF patients, and healthy controls. Tukey's test was used for post-hoc analysis. In order to control for differences in age, sex, and educational level between the two samples, analysis of covariance (ANCOVA) was applied. Effect sizes (i.e. standardized differences between two mean scores) were calculated by means of Cohen's *d*. By convention effect sizes are defined as "small, $d = .2$," "medium, $d = .5$," and "large, $d = .8$". Logistic regression was used to determine whether stroke patients were at increased risk of having symptoms of fatigue as compared to healthy controls. All analyses were performed using SPSS version 15.0.1.1.

RESULTS

Reliability and construct validity of the FAS in stroke patients

The internal consistency (α) of the FAS was .77 both at baseline, and at 2-month follow-up. Test-retest reliability was .81 for a 2-month interval. The PCA on the combined pool of FAS and BDI items revealed two factors (Table 1). Two FAS items loaded higher on the BDI component (FAS-8: no desire to do things; FAS-6: problems starting), while the BDI item on fatigue loaded higher on the FAS component. Overall, the FAS and the BDI represent two separate scales that measure fatigue and depression as different concepts. However, the component solution in Table 1 suggests that the FAS may not be a unidimensional construct in stroke patients because 4 out of 10 items either had low component loadings (FAS-3; FAS-7) or loaded on the BDI component (FAS-8; FAS-6). Therefore, more research on the content validity of the FAS is required in a larger sample of stroke patients. The association between the FAS and the BDI was .44 ($p<.001$).

Table 1. Component Loadings of the Fatigue and Depression Measures*

Item description	Component 1	Component 2
BDI-2: despondent about future	**.72**	.09
BDI-6: disappointed	**.69**	-.01
BDI-3: failure	**.69**	.11
BDI-4: not enjoying things	**.64**	.29
BDI-1: sad	**.64**	-.06
BDI-8: interest in others	**.59**	-.10
BDI-10: appearance	**.57**	-.01
FAS-8: no desire to do things	**.50**	-.06
FAS-6: problems starting	**.46**	-.19
BDI-11: activity	**.41**	-.02
BDI-5: guilty	**.38**	-.08
BDI-9: taking decisions	**.37**	-.02
BDI-13: appetite	.09	-.01
FAS-1: bothered by fatigue	-.13	**-.87**
FAS-2: tired quickly	-.14	**-.88**
FAS-5: physically exhausted	.05	**-.84**
BDI-12: fatigue	.15	**-.68**
FAS-9: mentally exhausted	.22	**-.64**
FAS-4: enough energy	.15	**-.58**
FAS-10: concentrate well	.16	**-.42**
FAS-3: don't do much	-.05	-.26
FAS-7: problems thinking clearly	.01	-.20

* loadings ≥.35 are displayed in bold

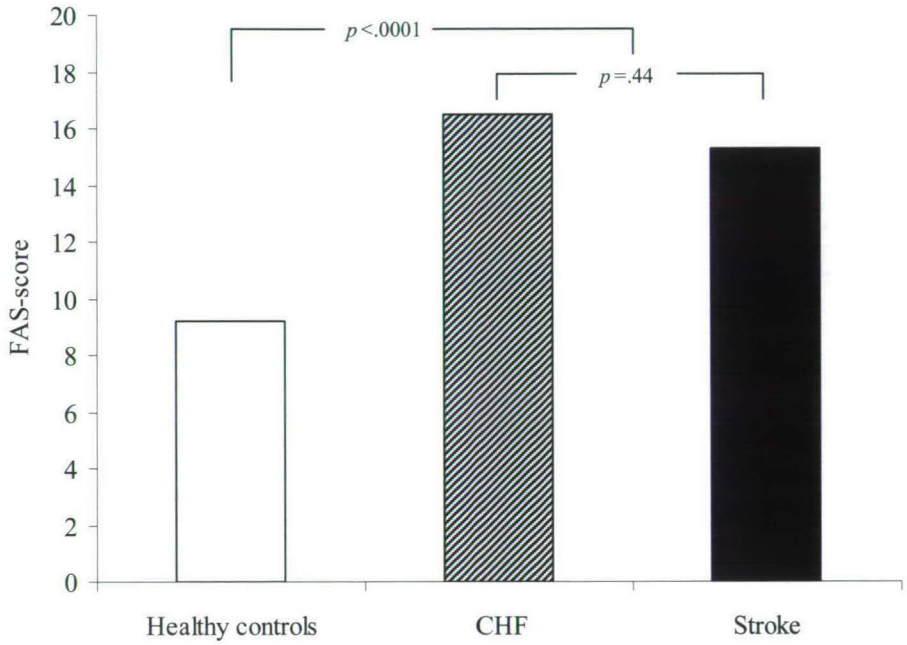
Fatigue levels in stroke patients, CHF patients, and healthy controls

As displayed in Figure 1, stroke patients (15.3 ± 7.6) and CHF patients (16.5 ± 7.9) reported similar levels of fatigue (p=.44). The level of fatigue was considerably higher in stroke patients and CHF patients as compared to healthy controls (9.2 ± 5.6; p<.001). Controlling for age, sex, and educational level did not alter these results. Moreover, computation of Cohen's d revealed that the effect sizes for stroke and CHF were large as compared to the effect sizes for gender and educational level (Figure 2). This result confirms the clinical relevance of stroke as a determinant of fatigue.

Next, levels of fatigue were dichotomized using the highest quintile of the healthy controls (FAS<12 = 0; FAS≥13 = 1). Accordingly, the prevalence of increased fatigue was 61.3% (n=49) for stroke patients, and 67.3% (n=92) for CHF patients. Using the healthy controls as a reference group, multivariable logistic regression revealed that stroke patients were at a 6-fold increased risk (OR=6.18; 95%CI 3.31-11.55, p<.001), and CHF patients were at an 8-fold

increased risk (OR=8.03; 95%CI 4.63-13.94, $p<.001$) for having symptoms of fatigue.

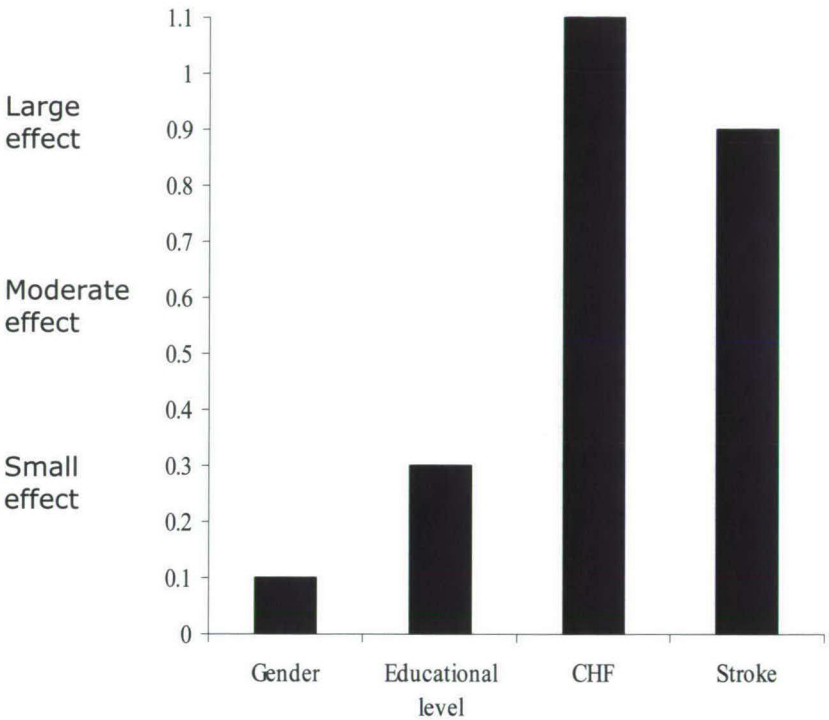
Figure 1. Mean level of fatigue stratified by medical condition



Disability as a predictor of fatigue in stroke patients

The four subscales of the SA-SIP30 were forced into a multivariable model with fatigue as the dependent variable. Logistic regression revealed that higher scores on the ambulation (OR=1.03; 95%CI 1.00-1.05, $p=.03$) and alertness behavior (OR=1.04; 95%CI 1.02-1.07, $p<.001$) subscales were associated with an increased risk of fatigue. The subscales body care and movement, and mobility were not associated with fatigue in this sample of stroke patients.

Figure 2. Effect size estimates indicating the clinical significance of gender, educational level, and medical condition as predictors of fatigue



DISCUSSION

This is the first study showing that levels of fatigue in stroke patients were as high as the levels in CHF patients, who experience fatigue as one of their main complaints. Levels in the stroke population were also significantly higher than levels in the normal population. Moreover, both stroke and CHF had a large effect on fatigue. These findings clearly emphasize the importance of fatigue in stroke patients. To measure fatigue, the FAS may be well applicable in stroke patients, since the FAS had good internal consistency as well as test-retest reliability in our stroke population. Moreover, the divergent validity of the FAS was good, since the FAS was found to measure fatigue and not depression. Only the unidimensionality of the FAS was questioned in our data. Disability levels partly explained fatigue in stroke patients.

Fatigue is a common complaint after stroke, although research has neglected this issue for years.(1-5) In our study, nearly two third of the patients experienced increased levels of fatigue 7.5 months after stroke. This is in line with previous studies, which reported a prevalence of fatigue between 39 and 72%.(2) Together with the notion that levels of fatigue in stroke patients were equal to the levels in CHF patients and both stroke and CHF had a large effect on fatigue, the issue of fatigue cannot be ignored in the stroke population. In addition, the impact of fatigue on quality of life and prognosis needs to be determined. Previous studies have shown an association between fatigue and increased dependency in activities of daily living(5) and decreased health related quality of life(16). Only one study researched the relationship between fatigue and mortality and reported a significant association(5).

Recent research has recommended the FAS to measure fatigue in stroke patients.(6) These authors reported lower internal consistency, but otherwise good reliability and validity of the FAS. Our results are largely in line, with good validity and reliability, including the internal consistency. However, the unidimensionality of the FAS, which has been described in other populations(7,11,12), was not supported in our stroke population, since 4 out of 10 items had low loadings on the FAS-factor. Hence, fatigue in the stroke population may be different from fatigue in other populations. In addition, Mead et al(6) reported that the FAS measures different facets of fatigue. Clearly, more research on the internal consistency, as well as the content validity of the FAS is warranted, but also the use of larger samples, because this study was based on 80 patients and the Mead et al(6) study on 55 patients.

Considering that levels of fatigue are equally high in stroke and CHF patients and effect sizes were large, several implications for clinical practice emerged. First, recognition of fatigue in stroke patients is important. We and others(6) advocate the FAS, since it has sound psychometric properties and contains only 10 items. Second, treatment of fatigue is important, but only one clinical trial focused on the treatment of fatigue, showing that fluoxetine did not improve fatigue(17). In other studies, several treatments were proposed, including evaluation of current medications, screening for depression, minimizing sleep disturbances, exercise programs, and patient education(18).

More research is needed on the treatment of fatigue as well as on the efficacy of the treatment.

A limitation of this study is the relatively small sample size, by which we were unable to draw definitive conclusions concerning the content validity of the FAS. Also, the generalizability of the results to the stroke population may be limited due to the exclusion of patients, suffering among others from a reduced level of consciousness. Despite these limitations, results of this study are clear, indicating that levels of fatigue in stroke patients were as high as the levels in CHF patients, and that both the effect of stroke and CHF on fatigue was large.

In conclusion, levels of fatigue in stroke patients are equal to the levels of fatigue in CHF patients, who experience fatigue as one of their main complaints. Moreover, both stroke and CHF had a large effect on fatigue, emphasizing its clinical importance in stroke patients. The FAS is an adequate measure of fatigue in stroke patients, but the content validity of the FAS in these patients needs to be examined in future studies.

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CHAPTER 7:

Patient-rated changes in fatigue over a 12-month period predict poor outcome in chronic heart failure

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ABSTRACT

Background and objectives: Little is known about factors that are associated with changes in fatigue in chronic heart failure (CHF). Moreover, it is unclear whether these changes have prognostic impact. The aim of this study was to examine these issues. **Methods**: 387 CHF patients were assessed twice (at baseline and at 12-month follow-up) for exertion and general fatigue. Regression models were developed to assess whether baseline characteristics predicted changes in fatigue, and to assess the effect of changes in fatigue on cardiac events occurring beyond 12-month follow-up. **Results**: An increase in exertion fatigue over a 12-month period was predicted by higher left ventricular ejection fraction (p=.02) and cognitive-affective depressive symptoms (p=.03) at baseline, and not having a biventricular pacemaker shortly after baseline (p=.02), whereas an increase in general fatigue was only predicted by cognitive-affective depressive symptoms (p=.002). 143 patients (37%) experienced an event (readmitted=117; death=26). An increase in exertion fatigue was associated with a near 2-fold increased risk of adverse events beyond 12-month follow-up (HR=1.78; 95%CI 1.18-2.68, p=.006), while controlling for standard cardiac risk factors. **Conclusions**: Baseline clinical and psychosocial factors predicted changes in fatigue. Increased exertion fatigue independently predicted an increased risk of cardiac readmission or death.

INTRODUCTION

Fatigue is commonly reported by chronically ill patients [1-3]. In chronic heart failure (CHF), fatigue is one of the most prevalent and distressing symptoms, that is also associated with disease progression [4-7]. Nevertheless, research concerning the clinical relevance of self-reported fatigue in CHF may be underreported in the cardiovascular literature, which may partially be due its ambiguous nature.

Explaining fatigue in CHF has proven to be difficult [6,8]. Previous studies have shown that left ventricular function measures relate poorly to fatigue [9,10]. Nevertheless, fatigue has been explained by impaired skeletal muscle blood supply as a result of reduced cardiac output [11]. Recently, it has been suggested that chronic, low grade haemodynamic stress as seen in CHF may lead to dominance of catabolic processes. This in turn leads to skeletal myopathy, causing the sensation of fatigue [11,12]. However, it remains unclear to what extent these factors may fully explain individual differences in fatigue.

Previous studies have demonstrated patients' self-assessment of CHF symptoms to be independently associated with poor prognosis [13,14]. In addition, it was shown that self-assessed symptoms and New York Heart Association (NYHA) classification were not coherent [13], indicating that there was little agreement between the patient and physician rated CHF symptoms. Self-assessed fatigue may therefore provide useful additional information about the patients' clinical and prognostic status.

The dynamic nature of symptoms in general, and fatigue in particular makes it necessary to examine these symptoms prospectively over time. Efforts should be made to gain knowledge about subgroups of CHF patients that are at increased risk to develop worse fatigue status over time, thereby providing an opportunity for risk stratification and prevention. Moreover, the prognostic impact of changes in self-reported fatigue should be examined as well.

The aims of this study were: (1) to determine clinical, demographic, and psychological predictors of changes in fatigue over a 12-month period, and (2) to examine whether these changes in fatigue were predictive of adverse cardiac events occurring beyond 12 months in patients with systolic CHF.

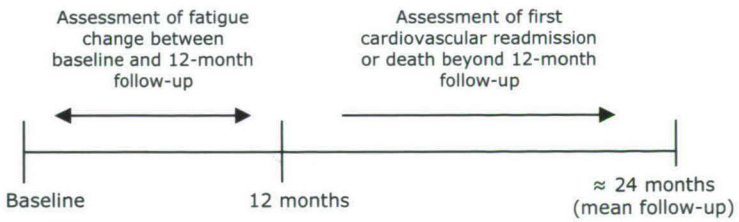
METHODS

Patients

The sample comprised 387 CHF patients (70.3% males; mean (SD) age = 66.4 (10.7) years; NYHA class III/IV = 42.9%) visiting the heart failure outpatient clinic of the TweeSteden Hospital, Tilburg, the Netherlands (see Table 1 for descriptives). Inclusion criteria were defined as systolic heart failure, LVEF≤40%, and sufficient understanding of spoken and written Dutch language. Exclusion criteria were defined as diastolic heart failure, age ≥ 80 years, myocardial infarction in the month prior to inclusion, and other life-threatening diseases.

Patients completed a questionnaire at baseline and at twelve-month follow-up. Information about cardiac readmission or death was collected beyond 12-month follow-up. The overall design of our study is shown in Figure 1. The hospital's medical ethics committee approved the study protocol, and the study was carried out according to the Helsinki Declaration. All patients provided written informed consent. Of the original 419 patients, 32 were excluded from the final analyses because they died between baseline and 12-month follow-up, hence, changes in fatigue could not be assessed.

Figure 1. Design of the study



Changes in fatigue

Previous research has suggested to differentiate between exertion and general fatigue; the former refers to fatigue directly related to the performing of activities in daily living [15], and the latter refers to an overwhelming,

sustained sense of exhaustion that does not necessarily have a relationship with exertion [16]. The Dutch Exertion Fatigue Scale (DEFS) assesses exertion fatigue by means of 9 items [15]. Items are answered with five response alternatives ranging from 0 (no) to 4 (yes). Cronbach's alpha was good in the present study (α=.91). The Fatigue Assessment Scale (FAS) was used to assess general fatigue [17]. This questionnaire consists of 10 items, which are answered on a 5-point Likert scale, ranging from 1 (never) to 5 (always). In the present study, the reliability of this instrument was high (α=.90).

Changes in exertion and general fatigue were calculated by means of residualized change scores (Δexertion fatigue$_{res}$, Δgeneral fatigue$_{res}$). These change measures reflect the degree to which an individual increased or decreased more than would be expected given his or her *initial* status. Residualized change scores are preferable to simple change scores because they eliminate auto correlated error and regression to the mean effects [18].

Clinical events beyond 12-month follow-up

Patients' hospital medical records were used to assess whether patients had been readmitted for cardiovascular causes since 12-month follow-up. The same procedure was followed to assess mortality. Accordingly, the combined clinical endpoint was defined as cardiac hospital readmission or death. The mean duration of follow-up counting from 12 months after baseline was 782 days (range 1-1798 days).

Clinical correlates

Clinical variables included LVEF, NYHA class, aetiology of CHF, cardiac history, biventricular pacemaker status, smoking status, body mass index (BMI), six minute walking test, physical inactivity, co morbidities, and medication. Information on clinical variables was obtained from the patients' medical records and from the treating cardiologist. Socio-demographic information included sex, age, marital status, and educational level.

Symptoms of dyspnoea

Since dyspnoea is one of the core symptoms of CHF, it was included as a potential predictor of changes in fatigue. Symptoms of dyspnoea were

measured by a subscale of the Health Complaint Scale [19]. Items are answered on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely).

Symptoms of depression

Symptoms of depression were assessed by means of the Beck Depression Inventory (BDI) [20]. Each item is rated on a 0-3 scale. The BDI is a reliable and well-validated measure of depressive symptomatology [21,22], and is the most widely used self-report measure of depression. Since the somatic items of the BDI may be confounded by fatigue, only the cognitive-affective subscale was used [23].

Type-D personality

Personality was used as a potential determinant of changes in fatigue as well. Type D personality was assessed by means of the 14-item Type D Scale (DS14), which comprises two subscales, Negative Affectivity and Social Inhibition [24]. A standardized cut-off score ≥10 on both subscales classifies individuals as having a Type D personality. Both scales have good internal reliability (α=.88 and .86, respectively), and are stable over time [24,25].

Statistical analyses

Prior to statistical analyses, educational level, marital status, NYHA-class, aetiology of heart failure, co-morbidities, and cardiac history were recoded into dichotomous variables. At 12-month follow-up, 19.4% of the DEFS scores and 19.1% of the FAS scores were missing. Simply discarding those patients wastes potential information and could bias results. Therefore, SAS procedure MI (multiple imputation) was used to create ten data sets to estimate values for missing data. After ordinary analysis, SAS procedure MIANALYZE was used to combine the results of the ten datasets [26,27].

SAS procedure REG was used to determine predictors of changes in fatigue. All baseline variables were forced into a multivariable model predicting respectively changes in exertion fatigue and changes in general fatigue. Cox proportional hazards regression, by means of the SAS procedure PHREG, was used to assess whether changes in fatigue predicted the combined end-point of

cardiovascular readmission or death beyond the 12 month follow-up. In multivariable analysis, we included standard cardiac risk factors (age, gender, smoking, BMI, physical inactivity, hypertension, hypercholesterolemia, and diabetes), measures of disease severity (LVEF, NYHA-class), and variables that predicted changes in fatigue.

RESULTS

Baseline characteristics

Of all included patients, 32 died between baseline and 12 month follow-up and were excluded from further analysis. Patients who completed the study differed systematically from patients who died within 12 months after baseline. Patients who died were more likely to be older (t=2.76, df=419; p=.006), male (χ2=4.31, df=1; p=.04), physically inactive (χ2=4.06, df=1; p=.04), and were more likely to be in NYHA-class III/IV (χ2=6.02, df=1; p=.01). In addition, they had lower ejection fraction (t= -2.83, df=404; p=.005), and lower exercise capacity (t= -4.11, df=413; p<.001). Baseline levels of both exertion (t=3.18, df=415; p=.002) and general fatigue (t=2.14, df=413; p=.03) were significantly higher in patients that died between baseline and 12 months follow-up as compared to patients who completed the study. Baseline characteristics of the sample included in final analyses (n=387) are displayed in Table 1.

Predictors of changes in fatigue

Multiple regression analysis revealed that changes in exertion fatigue over a 12-month period were predicted by LVEF, implementation of a BVP, beta-blockers, and cognitive-affective depressive symptoms. Patients having a higher LVEF, having more cognitive-affective depressive symptoms, not having a BVP, and not using beta-blockers were more likely to have an increase in exertion fatigue at 12-month follow-up. Changes in general fatigue were only predicted by cognitive-affective depressive symptoms. Patient with higher levels of depressive symptoms showed a greater increase in general fatigue at 12-month follow-up as compared to patients with lower levels of depressive symptoms (Table 2).

Table 1. Baseline characteristics

Age (SD)	66.4 (10.7)
Male gender, % (n)	70.3 (272)
Low educational level , % (n)	33.3 (129)
Having a partner, % (n)	70.8 (274)
Smoking, % (n)	23.0 (89)
Body Mass Index (SD)	28.6 (12.0)
Physical inactivity, % (n)	44.2 (171)
LVEF (SD)	30.7 (6.8)
NYHA-class III/IV, % (n)	42.9 (166)
Ischemic aetiology, % (n)	54.5 (211)
Hypertension, % (n)	39.8 (154)
Hypercholesterolemia, % (n)	47.5 (184)
Diabetes, % (n)	23.8 (92)
Co-morbidity, % (n)*	38.0 (147)
Implementation of BVP, % (n)†	9.3 (36)
Cardiac history, % (n)‡	57.4 (222)
ACE-inhibitors, % (n)	73.1 (283)
Diuretics, % (n)	72.6 (281)
Beta-blockers, % (n)	66.9 (259)
Statins, % (n)	49.9 (193)
Aspirin, % (n)	42.9 (166)
Psychotropic medication, % (n)	13.2 (51)
Six minute walking test (SD)	276.3 (159.6)
Symptoms of dyspnoea (SD)	2.4 (2.2)
Cognitive-affective depressive symptoms (SD)	1.3 (2.8)
Type-D personality, % (n)	19.6 (76)

* Stroke, COPD, peripheral arterial disease, liver disease, renal insufficiency

† Implementation of a biventricular pacemaker shortly after baseline

‡ History of MI, CABG, PCI

Table 2. Multivariable predictors of change in fatigue*

Variable	β	***p*-value**
Exertion fatigue		
LVEF	0.13	.02
Implementation of BVP	-0.14	.03
Beta-blocker	-0.11	.05
Cognitive-affective depressive symptoms	0.17	.02
General fatigue		
Implementation of BVP	-0.12	.09
Statins	-0.13	.07
Cognitive-affective depressive symptoms	0.20	.002

*Only variables with $p<.10$ are reported

Note: BVP: biventricular pacemaker, LVEF: left ventricular ejection fraction

Changes in fatigue and hospital readmission/death

As indicated before, the composite endpoint was defined as cardiac hospital readmission or death that occurred beyond 12-month follow-up. The mean duration of follow-up counting from 12 months after baseline was 782 days (range 1-1798 days). Over the period of follow-up, 143 patients (37%) experienced an event (readmitted=117; death=26).

In univariable analysis, both an increase in general fatigue (HR=1.04; 95%CI 1.00-1.07, p=.03) and exertion fatigue (HR=1.04; 95%CI 1.01-1.07, p=.005) were associated with an increased risk of cardiovascular readmission or death. In multivariable analysis, we controlled for the variables listed in Table 3. Accordingly, increased exertion fatigue was an independent predictor of cardiovascular readmission or death (HR=1.04; 95%CI 1.00-1.07, p=.03). Smoking (HR=1.58; 95%CI 1.08-2.32, p=.02), BMI (HR=1.01; 95%CI 1.00-1.02, p=.04), and diabetes (HR=1.61; 95%CI 1.09-2.36, p=.02) also predicted cardiovascular readmission or death. General fatigue did not predict clinical events in multivariable analysis.

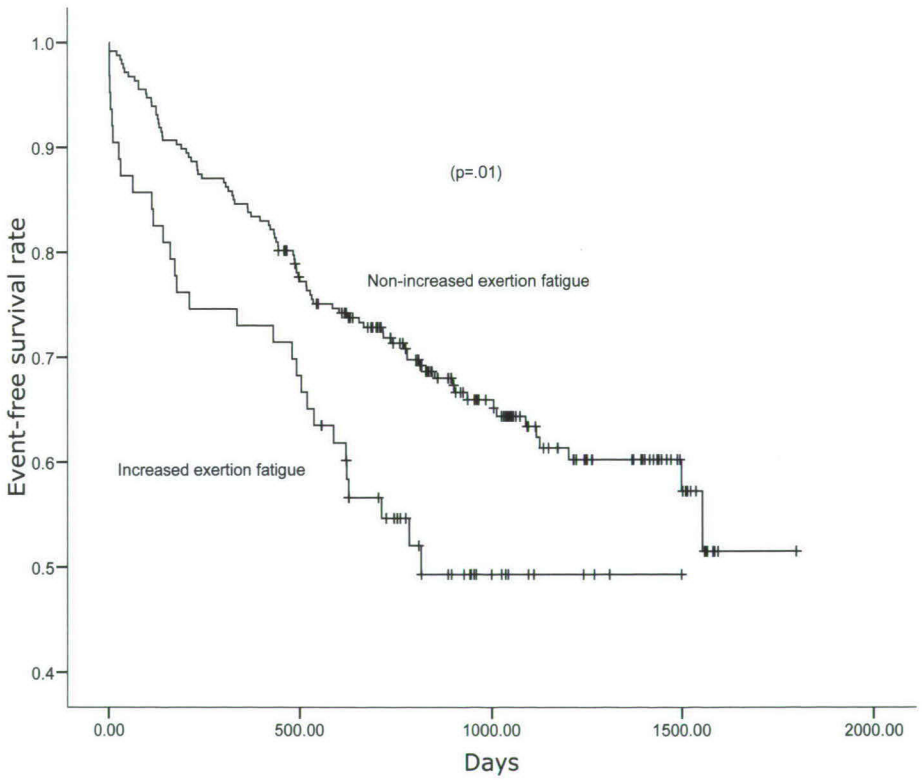
Table 3. Multivariable predictors of cardiovascular readmission or death

Variable	HR	95%CI	*p*-value
Age (SD)	1.00	0.98-1.01	.72
Male gender	1.46	0.97-2.21	.07
Hypertension	0.82	0.58-1.17	.28
Hypercholesterolemia	0.99	0.68-1.45	.97
Smoking	**1.58**	**1.08-2.32**	**.02**
Body Mass Index	**1.01**	**1.00-1.02**	**.04**
Physical inactivity	1.16	0.82-1.65	.40
Diabetes	**1.61**	**1.09-2.36**	**.02**
LVEF (SD)	0.99	0.97-1.02	.49
NYHA-class III/IV	1.37	0.95-1.96	.09
Statins	1.17	0.80-1.73	.42
Beta-blocker	0.92	0.64-1.33	.67
Implementation of BVP	0.62	0.30-1.28	.19
Cognitive-affective depressive symptoms	1.00	0.94-1.06	.94
ΔGeneral fatigue$_{res}$	1.01	0.97-1.05	.59
ΔExertion fatigue$_{res}$	**1.04**	**1.00-1.07**	**.03**

Note: BVP: biventricular pacemaker, LVEF: left ventricular ejection fraction

Next, Δexertion fatigue$_{res}$ was dichotomized using the highest quintile (Δexertion fatigue$_{res}$<5 = 0; Δexertion fatigue$_{res}$ ≥5 = 1). Accordingly, the event rate was 34% (n=104) in the non-increased exertion fatigue group, and 46% (n=39) in the increased exertion fatigue group. The Kaplan-Meier curve in Figure 2 shows that patients in the increased exertion fatigue group were more likely to experience an event as compared to patients in the non-increased exertion fatigue group (p=.01). Multivariable analysis revealed that patients in the increased exertion fatigue group had a near 2-fold increased risk of experiencing an adverse event (HR=1.78; 95%CI 1.18-2.68, p=.006).

Figure 2. Event-free survival rate of cardiovascular readmission or death for exertion fatigue



DISCUSSION

To the best of our knowledge, this is the first study to examine the predictors of changes in fatigue over time in CHF patients and to examine the prognostic impact of these changes in fatigue in CHF. An increase in exertion fatigue over a 12-month period was predicted by higher LVEF and cognitive-affective depressive symptoms at baseline, and by not having implementation of a BVP shortly after baseline. An increase in general fatigue was only predicted by cognitive-affective depressive symptoms.

Increased exertion fatigue at 12 months follow-up were independently associated with an increased risk of cardiovascular readmission or death beyond 12 months follow-up, whereas an increase in general fatigue was only associated with adverse outcome in univariable analysis. These results are in line with studies that show that fatigue in CHF [7,13,14], and increased fatigue in coronary patients [28] are associated with adverse outcomes.

Fatigue is considered to be one of the most important factors in affecting the patients' quality of life, and there is growing need for adequate clinical management of fatigue [29,30]. Nonetheless, little is known about why patients experience fatigue [31], and explaining individual differences in fatigue has proven to be difficult [6]. The current study identified factors that contribute to change in fatigue over time in CHF patients. In accordance with previous work [32], implementation of a BVP was associated with a decrease in exertion fatigue. Changes in both exertion fatigue and general fatigue were predicted by cognitive-affective depressive symptoms at baseline. This result extends our previous findings [8], and lends further support to the possible role of depression in the perception and reporting of disease specific symptoms in CHF [8]. The association between higher LVEF and increased exertion fatigue was counterintuitive but it could be that better status on both LVEF and exertion fatigue at baseline is more likely to deteriorate than if either or both are already significantly impaired .

The current study emphasizes the importance of recognizing changes in fatigue in clinical practice. Recognition of these changes allows health care professionals to act on this, for example by offering exercise training. The importance of exercise training was recently reviewed in a meta-analysis by Puetz et al [33], in which they showed that cardiac rehabilitation exercise

programs have considerable effects on levels of energy and fatigue. However, it remains unclear whether improvement after therapy is associated with improved prognosis. Future studies should address this issue.

In addition, the mechanisms through which fatigue exert its negative effects are unclear. We hypothesize that mechanisms are different for exertion fatigue and general fatigue. Exertion fatigue may primary reflect the direct physical consequences of the disease itself, and an increase of exertion fatigue may therefore reflect worsening of CHF. Future studies should assess physiological measures that are known to be abnormal in CHF patients and that are relevant with respect to fatigue, for example measures of abnormal muscle metabolism and an enhanced ergo reflex response [11,12]. Future studies should measure in parallel changes in exertion fatigue and such physiological parameters. On the other hand, general fatigue may reflect the more psychological consequences of CHF and may, to some extent, be on par with mental fatigue. A hint towards this association was given by the fact that the increase in general fatigue was predicted only by cognitive-affective depressive symptoms. Increased general fatigue may therefore have impact on the patients' ability for self-care, which has been associated with poor prognosis in CHF [34].

There is also some evidence that vital exhaustion, a concept related to general fatigue, is associated with increased levels of inflammatory markers in patients with coronary heart disease [35,36]. These cytokines have been associated with adverse outcomes in CHF [37-39]. Indeed, one important sign of peripheral inflammatory signals is fatigue and behavioural withdrawal [40], as part of the sickness response. Further research into the mechanisms responsible for the link between fatigue and CHF prognosis is warranted in order to optimize treatment strategies. Given the failure of anti-TNF medication to improve prognosis in CHF [41], and if increases in fatigue are found to be related to proinflammatory cytokines, such interventions may be more effective if provided specifically to patients with worse fatigue.

This study had a number of limitations. First, there may have been a bias in the selection of patients. The cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern might have influenced selection. Second, we used combined endpoints in order to increase

the number of clinical events, and did not use mortality as a separate endpoint. Factors predicting readmission may differ from those predicting death. Third, we did not have data available on changes in variables other than fatigue. For future studies, it would be interesting to determine whether changes in cardiac function, renal function, 6-minute walk test or peak oxygen consumption are related to changes in fatigue. Fourth, we did not have information on diagnosis of major depression. Nevertheless, the strengths of the current study were the repeated assessment of fatigue over time, and the prospective design examining the impact of these changes in fatigue on prognosis. Finally, we used reliable and valid measures of both exertion and general fatigue.

In summary, changes in fatigue were related to clinical and psychosocial factors, and increased exertion fatigue independently predicted an increased risk of cardiac readmission or death. The current study contributes to the understanding of fatigue in CHF, and reveals that changes in fatigue are of clinical and prognostic importance. Taking symptom changes into account, in addition to their biomedical and psychosocial predictors, may lead to improved risk stratification and clinical management in this high-risk patient group.

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CHAPTER 8:

Distinct trajectories of fatigue in chronic heart failure and their association with prognosis

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Submitted for publication

ABSTRACT

Aim: Fatigue is a poorly understood symptom in chronic heart failure (CHF). We examined the different trajectories of fatigue over a 12-month period and their impact on mortality in CHF. **Methods:** Consecutive CHF patients (N=310) were assessed at baseline, 2- and, 12-month follow-up for symptoms of exertion and general fatigue. Latent growth mixture modelling was used to examine the course of fatigue over time. The endpoint was mortality following the 12-month assessment of fatigue. **Results:** Over the initial 12-month follow-up, 6 distinct trajectories for exertion fatigue and 4 distinct trajectories for general fatigue were identified. Age, sex, exercise capacity, physical inactivity, somatic comorbidities, and psychotropics use were significant predictors of these trajectories. Beyond the 12-month follow-up (mean follow-up period 693 days), 50 patients (17%) had died. Compared to the reference group, both severe exertion fatigue (HR=2.59; 95%CI 1.09-6.16, p=.03) and severe general fatigue (HR=3.20; 95%CI 1.62-6.31, p=.001) independently predicted an increased mortality rate (29% vs. 19% and 28% vs. 14%, respectively). Low exertion fatigue was associated with a decreased mortality rate (3% vs. 19%; HR=0.12; 95%CI 0.02-0.93, p=.04). **Conclusions:** Fatigue trajectories varied across CHF patients, and had a differential effect on mortality. Persistent severe fatigue was a predictor of poor prognosis. These results may help identify distinct groups of CHF patients with potentially differential risks of adverse health outcomes.

INTRODUCTION

Fatigue is considered one of the key symptoms in chronic heart failure (CHF), as symptoms of fatigue to a large extent determine the patient's quality of life (1). Moreover, it has also been suggested that symptoms of fatigue may be associated with poor cardiovascular outcomes in CHF (2-5).

Research on fatigue in CHF has primarily focused on its pathophysiological underpinnings (6,7), and its determinants (3,8-13). It has been suggested that chronic, low grade haemodynamic stress as seen in CHF may lead to dominance of catabolic processes, which in turn leads to skeletal myopathy, causing the sensation of fatigue (6,7). Other studies have identified symptoms of dyspnoea, symptoms of depression, and personality factors as important determinants of fatigue in CHF (11-14). Nonetheless, fatigue is still beyond complete comprehension, and it is unlikely that the factors mentioned above fully explain individual differences in fatigue.

Fatigue is highly prevalent among CHF patients, and progression of CHF is on par with an increase in symptoms of fatigue (1,3,4,11). However, the evolution of fatigue over time is not the same for all patients with CHF. It may be important to distinguish distinct developmental trajectories of fatigue in CHF, as knowledge of fatigue trajectories, their clinical and psychological determinants, and their prognostic impact allow for the identification of high-risk CHF patients who may need additional clinical care above and beyond the standard medical management of the disease.

Since the course of fatigue has not been studied in CHF patients, the currents study's objective was to examine 1) the course and predictors of symptoms of fatigue in CHF during a 12-month period, and 2) their prognostic impact beyond the 12-months follow-up.

METHODS

Patients

This study included 310 CHF patients with systolic heart failure and a left ventricular ejection fraction (LVEF) ≤40%, visiting the heart failure outpatient clinic of the TweeSteden hospital, Tilburg, the Netherlands. Of the 378 patients that were initially included, 44 patients died during the first year of the study, and 24 patients had missing questionnaire data on 2 or more

measurement points, leaving 310 patients for the present study. Patients with diastolic heart failure, age ≥80 years, myocardial infarction in the month prior to inclusion, other life-threatening diseases, and no or insufficient understanding of spoken and written Dutch language were excluded on beforehand.

Patients completed a questionnaire at baseline, 2-month follow-up, and 12-month follow-up. The study protocol was approved by the local medical ethics committee in Tilburg, the Netherlands. The study was conducted conform to the Helsinki Declaration and every patient provided written informed consent.

Symptoms of fatigue

Previous research suggests to differentiate between exertion and general fatigue (5,12),the former referring to fatigue directly related to the performing of activities in daily living, and the latter to an overwhelming, sustained sense of exhaustion that does not necessarily have a relationship with exertion. The Dutch Exertion Fatigue Scale (DEFS) assesses exertion fatigue by means of 9 items (15). Items are answered with five response alternatives ranging from 0 (no) to 4 (yes). Chronbach's alpha is high (α=91). The Fatigue Assessment Scale (FAS) was used to assess symptoms of general fatigue (16). This questionnaire consists of 10 items, which are answered on a 5-point Likert scale, ranging from 0 (never) to 4 (always). The reliability of this instrument is high (α=.90).

Demographic and clinical variables

Demographic variables included sex, age, marital status, and educational level. Clinical variables comprised LVEF, NYHA functional class, CHF etiology, diabetes mellitus, hypertension, hypercholesterolemia, co-morbidities (stroke, chronic obstructive pulmonary disease, peripheral arterial disease, renal insufficiency), cardiac history (MI, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)), smoking status, physical inactivity, body mass index (BMI), cardiac medication, and psychotropic medication. Exercise capacity was measured by means of the six-minute walking test (SMWT - walking small circuits of 52 meters), which was carried

out within the hospital as part of this study. Patients were instructed to walk at a normal pace, and to continue walking until they were told to stop or until they experienced too many adverse symptoms. Patients were not encouraged to walk as far as possible because the test was meant to reflect daily life exercise capacity. Information on clinical variables was obtained from the medical records and from the treating cardiologist or heart failure nurse.

Mortality beyond 12-month follow-up

Patients' hospital medical records were used to assess mortality since 12-month follow-up. The mean duration of follow-up counting from 12 months after baseline was 693 days (range 74 -1516 days).

Statistical analyses

Prior to statistical analyses, age (<60 yrs vs. ≥60 yrs), educational level (low vs. higher), marital status (partner vs. no partner), LVEF (<30% vs. ≥30%), NYHA functional class (I/II vs. III/IV), CHF etiology (ischemic vs. non-ischemic), co-morbidities (present vs. not present), cardiac history (present vs. not present), and exercise capacity (<300 meters vs. ≥300 meters) were recoded into dichotomous variables.

Latent class regression analysis was employed to examine trajectories of fatigue symptoms in CHF patients over a 12-month period (17). A finite mixture model was fit to identify classes of individuals following similar patterns of behavior over time. The model assumes unobserved latent variables to explain the associations among observed scores, and can be seen as a categorical equivalent of factor analysis. One of the problems with fitting these types of latent class models is that the categorization into classes is dominated by the overall symptom levels which makes it less likely that the model picks up symptom changes. A way to overcome this problem is the inclusion of a random intercept (18).

To determine the optimal number of trajectories, the Aiken Information Criterion 3 (AIC3) was used, with a higher AIC3 indicating a better fit. However, a difference of less than 3 will favor the least complex model. Recent studies have shown that AIC3 is a better criterion than BIC and AIC in determining the number of latent classes in LC models (19,20).

For comparison between classes we used the Chi-square test for discrete variables. Adjusted Standardized Residuals (ASRs) were used to identify groups responsible for significant differences. A residual greater than 2.0 was taken to indicate a significantly higher frequency, and a residual less than -2.0 was considered to indicate a significantly lower frequency, than expected if the independence hypothesis was true (21). Variables that were significant in the univariate Chi-square analyses were entered into a multivariate multinomial logistic regression model to assess whether demographic, medical, and psychological variables were predictors of trajectories of symptoms of fatigue.

Cox proportional hazards regression was used to assess whether fatigue trajectories predicted mortality beyond 12-month follow-up. In multivariate Cox regression, we included age, gender, BMI, physical inactivity, diabetes mellitus, and a measure of disease severity (LVEF) because of their relation with cardiovascular prognosis and fatigue. The LC cluster analysis was performed with the LCA program Latent GOLD (17). All other data were analyzed using SPSS 15.0.1 for Windows. A similar approach has previously been used in MI- (22), PCI- (23), and PAD patients (14).

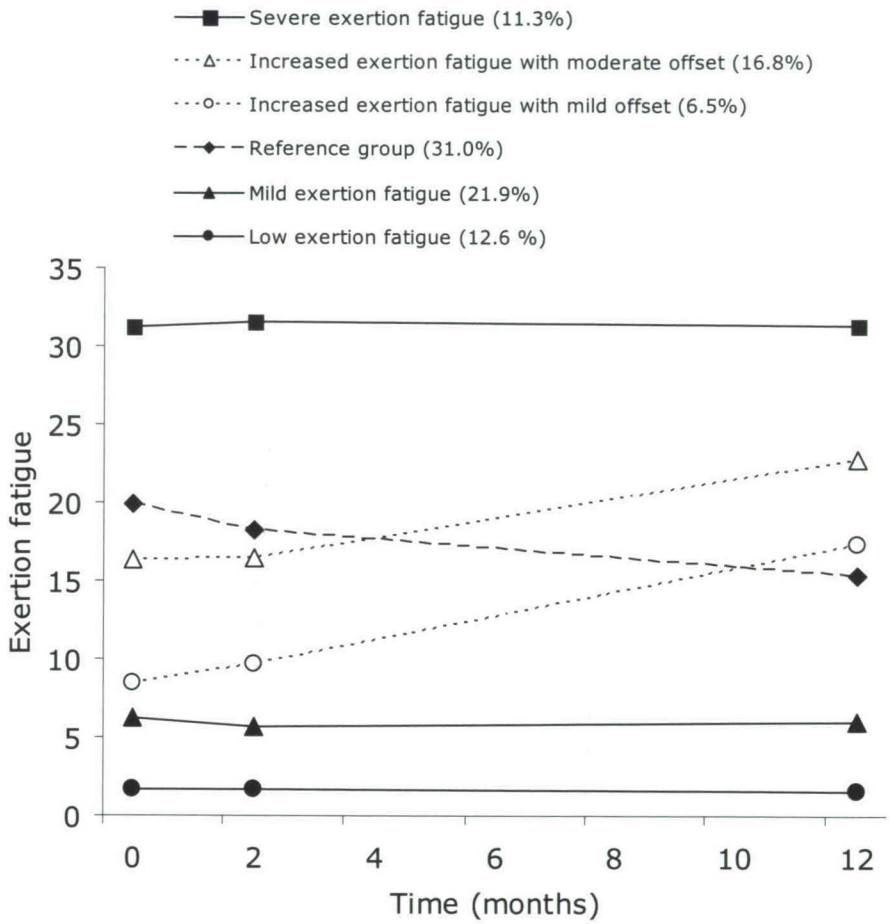
RESULTS

Trajectories of exertion fatigue

Figure 1 displays the six distinct developmental trajectories for exertion fatigue. The AIC3 improved from one class of exertion fatigue (AIC3 = -6353) to six classes of exertion fatigue (AIC3 = -5899), whereas a relative decline was observed in the seven class model (AIC3 = -5903). Compared to the five class model (AIC3 = -5915), the six class model achieved a significant improvement in fit. The six class model was therefore adopted for further analysis.

The first class (12.6% of the sample) was classified as the low exertion fatigue group and was stable of time (intercept=1.69, $p<.001$; slope= -0.0054, $p=.76$). The level of exertion fatigue in the second class (21.9%) was slightly higher than in the first class and stable over time (intercept=5.91 , $p<.001$; slope= -0.011, $p=.72$), and was therefore classified as the mild exertion fatigue group. Class three (31.0%) had a moderate offset with an observed

Figure 1. Observed trajectories of exertion fatigue



mean DEFS-score at baseline of 19.94 (95%CI: 18.61-21.27) but showed a significant decrease of exertion fatigue over time (intercept=18.87, $p<.001$; slope= -0.28, $p=.004$). Since the third class comprises the largest group of patients it was conceptualized as the reference group in the present study. The fourth class (6.5%) was described as increasingly fatigued with a mild offset (observed mean baseline DEFS-score = 8.40, 95%CI: 6.50-10.30; model intercept=8.07, $p<.001$; slope=0.74, $p<.001$). Class five (16.8%) had an increase of exertion fatigue and a moderate offset (observed mean baseline DEFS-score = 16.33, 95%CI: 14.06-18.60; model intercept=17.03, $p<.001$;

slope=0.31, p=.05). Finally, the sixth class (11.3%) was classified as severely fatigued across all assessment points (intercept=31.45, p<.001; slope= -0.006, p=.92).

Trajectories of general fatigue

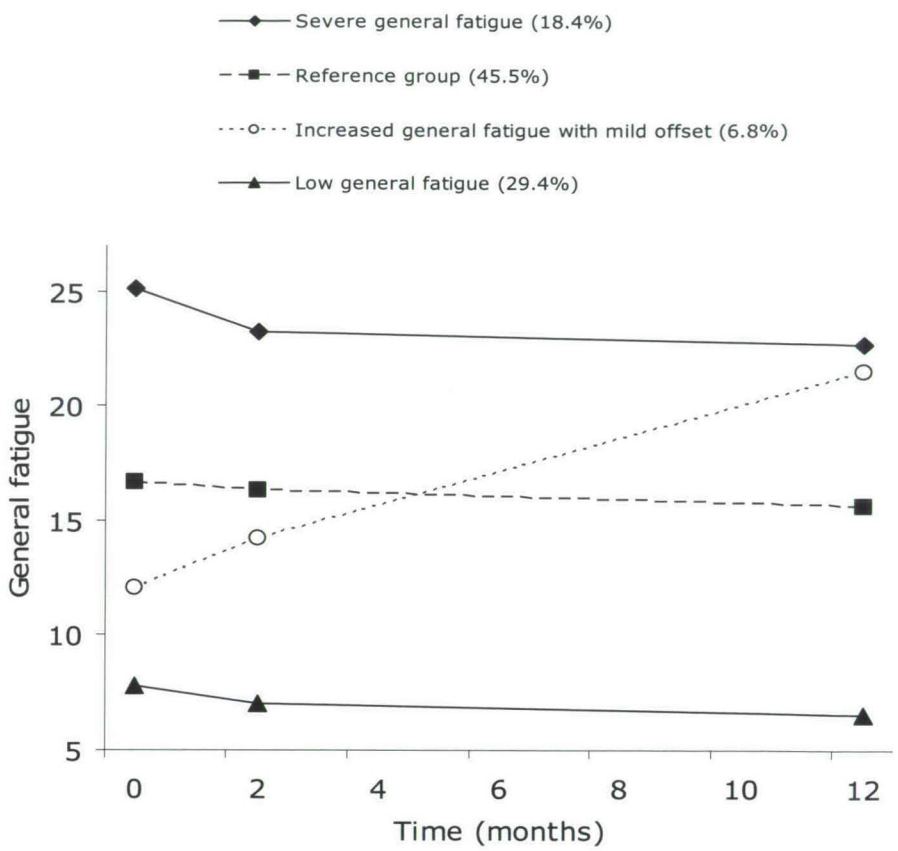
The levels of general fatigue were relatively stable over time for most patients (Figure 2). The AIC3 improved from one class of general fatigue (AIC3 = -5863) to four classes of general fatigue (AIC3 = -5741), whereas a relative decline was observed in the five-class model (AIC3 = -5749). Compared to the three-class model (AIC3 = -5745), the four-class model achieved a significant improvement in fit. A four class model for general fatigue was therefore adopted for further analysis.

The first class (29.4% of the sample) was classified as the low general fatigue group and was stable over time (intercept=8.55, p<.001; slope= -0.095, p=.06). The second class (45.5%) had fairly stable moderate levels of fatigue, and was conceptualized as the reference group since this class comprises the largest group of patients (intercept=15.10 , p<.001; slope= -0.090, p=.04). The third class (6.8%) was described as increasingly fatigued with a mild offset (observed mean baseline FAS-score = 12.05, 95%CI: 9.84-14.26; model intercept=13.13, p<.001; slope=0.71, p<.001). Finally, the fourth class (18.4%) was classified as severely fatigued across all assessment points (intercept=22.50, p<.001; slope= -0.10, p=.06).

Baseline characteristics stratified by fatigue class

There were a number of differences in demographic, clinical, and psychological characteristics at baseline as a function of exertion fatigue class (Table 1) and general fatigue class (Table 2). Departure from independence was most pronounced in the extreme exertion fatigue groups, (Table 1; numbers in bold). Patients in the low exertion fatigue group were younger (ASR= -3.6), and less likely to be obese (ASR= -2.2), diabetic (ASR= -2.9), low on exercise capacity (ASR= -4.2), in a higher NYHA-class (ASR= -3.3), or to be on diuretics (ASR= -2.5). Patients in the severe exertion fatigue group were more likely to be female (ASR=2.9), obese (ASR=2.0), physically inactive (ASR=5.0), to have comorbidities (ASR=2.1), low exercise capacity (ASR=6.3),

Figure 2. Observed trajectories of general fatigue



to be on diuretics (ASR=2.6), or psychotropic medication (ASR=5.7), and to be in higher NYHA-class (ASR=3.8).

Regarding general fatigue groups, departure from independence was only observed in the low and the severe fatigue groups (Table 2: numbers in bold). Patients in the low general fatigue group were less likely to be physically inactive (ASR= -2.6), to be in higher NYHA-class (ASR= -2.2), to be on psychotropic medication (ASR= -2.8), and to have low exercise capacity (ASR= -4.0). Patients in the severe general fatigue were more likely to be smokers (ASR=3.2), to be physically inactive (ASR=4.3), in a higher NYHA-class (ASR=2.0), and to have low exercise capacity (ASR= 3.1).

Table 1. Baseline characteristics stratified by exertion fatigue class*

Variable	Total	Low exertion Fatigue (n=39)	Mild exertion fatigue (n=68)	Reference group (n=96)	Increased exertion fatigue with mild offset (n=20)	Increased exertion fatigue with moderate offset (n=52)	Severe exertion fatigue (n=35)	*p*-value
Male sex	70.0 (217)	82.1 (32)	**85.3 (58)**	64.6 (62)	65.0 (13)	67.3 (35)	**48.6 (17)**	<.001
Age≥60	72.6 (225)	**48.7 (19)**	72.1 (49)	76.0 (73)	85.0 (17)	75.0 (39)	80.0 (28)	.01
Having no partner	71.3 (221)	79.5 (31)	80.9 (55)	66.7 (64)	60.0 (12)	69.2 (36)	65.7 (23)	.20
Low educational level	15.2 (47)	17.9 (7)	22.1 (15)	12.5 (12)	25.0 (5)	9.6 (5)	8.6 (3)	.21
Smoking	22.6 (70)	17.9 (7)	22.1 (15)	19.8 (19)	15.0 (3)	32.7 (17)	25.7 (9)	.44
Obesity (BMI>30)	27.7 (86)	**12.8 (5)**	20.6 (14)	**35.4 (34)**	20.0 (4)	28.8 (15)	**40.0 (14)**	.03
Ischemic etiology	53.9 (167)	46.2 (18)	54.4 (37)	60.4 (58)	35.0 (7)	51.9 (27)	57.1 (20)	.34
Cardiac history†	57.1 (177)	48.7 (19)	54.4(37)	60.4 (58)	45.0 (9)	55.8 (29)	71.4 (25)	.31
Physical inactivity	43.2 (134)	35.9 (14)	**23.5 (16)**	45.8 (44)	25.0 (5)	50.0 (26)	**82.9 (29)**	<.001
Hypertension	37.4 (116)	15.4 (6)	41.2 (28)	37.5 (36)	40.0 (8)	40.4 (21)	48.6 (17)	.06
Hypercholesterolemia	47.7 (148)	35.9 (14)	45.6 (31)	53.1 (51)	30.0 (6)	55.8 (29)	48.6 (17)	.20
Diabetes	23.9 (74)	**5.1 (2)**	23.5 (16)	27.1 (26)	15.0 (3)	**34.6 (18)**	25.7 (9)	.03
Comorbidities‡	35.2 (109)	23.1 (9)	26.5 (18)	**43.8 (42)**	20.0 (4)	34.6 (18)	**51.4 (18)**	.02
LVEF<30%	40.0 (124)	41.0 (16)	39.7 (27)	41.7 (40)	45.0 (9)	36.5 (19)	37.1 (13)	.98
NYHA-class III/IV	39.4 (122)	**15.4 (6)**	**25.0 (17)**	46.9 (45)	40.0 (8)	42.3 (22)	**68.6 (24)**	<.001
ACE-inhibitors	71.9 (223)	76.9 (30)	66.2 (45)	76.0 (73)	65.0 (13)	71.2 (37)	71.4 (25)	.72
Diuretics	73.2 (227)	**56.4 (22)**	73.5 (50)	76.0 (73)	80.0 (16)	65.4 (34)	**91.4 (32)**	.01
Beta blocker	68.7 (213)	79.5 (31)	69.1 (47)	69.8 (67)	80.0 (16)	55.8 (29)	65.7 (23)	.18
Statins	51.0 (158)	12.8 (5)	20.6 (14)	35.4 (34)	20.0 (4)	28.8 (15)	40.0 (14)	.45
Aspirin	43.5 (135)	48.7 (19)	50.0 (34)	43.8 (42)	30.0 (6)	34.6 (18)	45.7 (16)	.44
Psychotropic medication	12.6 (39)	5.1 (2)	**2.9 (2)**	12.5 (12)	5 (1)	13.5 (7)	**42.9 (15)**	<.001
SMWT<300m	41.6 (129)	**10.3 (4)**	**19.1 (13)**	49.0 (47)	30.0 (6)	51.9 (27)	**91.4 (32)**	<.001

* Numbers in bold represent an absolute adjusted standardized residual > 2.0
† History of MI, CABG, PCI
‡ Stroke, COPD, peripheral arterial disease, renal insufficiency

Table 2. Baseline characteristics stratified by general fatigue class*

Variable	Total	Low general Fatigue (n=91)	Reference Group (n=141)	Increased general fatigue with mild offset (n=21)	Severe general fatigue (n=57)	*p*-value
Male sex	70.0 (217)	75.8 (69)	70.2 (99)	66.7 (14)	61.4 (35)	.31
Age≥60	72.6 (225)	70.3 (64)	74.5 (105)	76.2 (16)	70.2 (40)	.85
Having no partner	71.3 (221)	74.7 (68)	72.3 (102)	57.1 (12)	68.4 (39)	.41
Low educational level	15.2 (47)	20.9 (19)	14.2 (20)	19.0 (4)	7.0 (4)	.13
Smoking	22.6 (70)	18.7 (17)	19.1 (27)	19.0 (4)	**38.6 (22)**	.02
Obesity (BMI>30)	27.7 (86)	24.2 (22)	27.7 (39)	28.6 (6)	33.3 (19)	.69
Ischemic etiology	53.9 (167)	47.3 (43)	57.4 (81)	47.6 (10)	57.9 (33)	.39
Cardiac history†	57.1 (177)	50.5 (46)	60.3 (85)	42.9 (6)	64.9 (37)	.15
Physical inactivity	43.2 (134)	**31.9 (29)**	40.4 (57)	42.9 (9)	**68.4 (39)**	<.001
Hypertension	37.4 (116)	35.2 (32)	37.6 (53)	38.1 (8)	40.4 (23)	.94
Hypercholesterolemia	47.7 (148)	42.9 (39)	49.6 (70)	57.1 (12)	47.4 (27)	.61
Diabetes	23.9 (74)	19.8 (18)	22.0 (31)	33.3 (7)	31.6 (18)	.26
Comorbidities‡	35.2 (109)	35.2 (32)	37.6 (53)	19 (4)	35.1 (20)	.43
LVEF<30%	40.0 (124)	37.4 (34)	42.6 (60)	38.1 (8)	38.6 (22)	.87
NYHA-class III/IV	39.4 (122)	**29.7 (27)**	40.4 (57)	42.9 (9)	**50.9 (29)**	.05
ACE-inhibitors	71.9 (223)	68.1 (62)	73.0 (103)	81.0 (17)	71.9 (41)	.66
Diuretics	73.2 (227)	67.0 (61)	75.9 (107)	71.4 (15)	77.2 (44)	.43
Beta blocker	68.7 (213)	73.6 (67)	68.1 (96)	61.9 (13)	64.9 (37)	.60
Statins	51.0 (158)	50.5 (46)	54.6 (77)	57.1 (12)	40.4 (23)	.30
Aspirin	43.5 (135)	38.5 (35)	46.8 (66)	57.1 (12)	38.6 (22)	.29
Psychotropic medication	12.6 (39)	**4.4 (4)**	15.6 (22)	9.5 (2)	19.3 (11)	.03
SMWT<300m	41.6 (129)	**24.2 (22)**	46.1 (65)	38.1 (8)	**59.6 (34)**	<.001

* Numbers in bold represent an absolute adjusted standardized residual > 2.0
† History of MI, CABG, PCI
‡ Stroke, COPD, peripheral arterial disease, renal insufficiency

Predictors of fatigue trajectories

Multivariate predictors of exertion fatigue trajectories are shown in Table 3. Multinomial logistic regression analysis revealed that younger patients, patients without diabetes mellitus or other comorbidities, and patients with a preserved exercise capacity were more likely to be in the low exertion fatigue class as compared to the reference group, whereas patients in NHYA-class III/IV were less likely to be in the low exertion fatigue class (Table 3a). Furthermore, male, physically active patients without comorbidities and impaired exercise capacity were more likely to be in the mild exertion fatigue class as compared to the reference group. Finally, female, physically inactive patients on psychotropic medication and with impaired exercise capacity were more likely to be in the severe exertion fatigue group (Table 3a).

Patients with a preserved exercise capacity and not on psychotropic medication were more likely to be in the low general fatigue class as compared to the reference group (Table 3b). In contrast, physically inactive, smoking patients were more likely to be in the severe general fatigue class. An additional analysis controlling for disease severity (LVEF) did not alter the results reported in Table 3.

Trajectories of fatigue and CHF prognosis

The mean follow-up period was 28.3 months (SD=11.8). During this period, 50 patients (16.6%) had died. Older age, being physically active and lower LVEF were associated with a higher incidence of mortality (Table 4). Obesity showed a trend towards significance. Of note, being physically active was only significantly associated with mortality in multivariate analysis, and may therefore represent a suppressor effect.

A first Cox regression model showed that both low exertion fatigue and severe exertion fatigue predicted mortality beyond 12-month follow-up (Table 4a, and Figure 3a). Compared to the reference group (mortality rate = 19%), patients in the low exertion fatigue class had a decreased mortality rate (3%; HR=0.12; 95%CI 0.02-0.93, p=.04), and patients in the severe exertion fatigue class an increased mortality rate (29%; HR=2.59; 95%CI 1.09-6.16, p=.03). A second Cox regression model showed that severe general fatigue predicted mortality beyond 12-month follow-up (Table 4b, and Figure 3b).

Patients in the severe general fatigue class had an increased risk for mortality as compared to the reference group (mortality rate = 28% vs. 14%; HR=3.20; 95%CI 1.62-6.31, p=.001).

Table 3. Multivariate predictors of fatigue class*

(3a) Exertion fatigue class

	Low exertion Fatigue		Mild exertion fatigue		Increased exertion fatigue with mild offset		Increased exertion fatigue with moderate offset		Severe exertion fatigue	
Variable	OR	*p*	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Male sex	2.56	.08	**3.32**	**.006**	ns	ns	ns	ns	0.40	.08
Age≥60	**0.35**	**.02**	ns	ns	ns	ns	ns	ns	ns	ns
Obesity, BMI>30	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Physical inactive	ns	ns	**0.41**	**.02**	ns	ns	ns	ns	**6.71**	**.001**
Diabetes	**0.21**	**.05**	ns	ns	ns	ns	ns	ns	ns	ns
Comorbidities†	**0.31**	**.02**	**0.44**	**.03**	0.33	.07	ns	ns	ns	ns
NYHA-cl. III/IV	**0.32**	**.04**	0.48	.06	ns	ns	ns	ns	ns	ns
Diuretics	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Psychotropics	ns	ns	0.22	.07	ns	ns	ns	ns	**5.43**	**.003**
SMWT<300m	**0.22**	**.02**	**0.39**	**.02**	ns	ns	ns	ns	**9.62**	**.001**

(3b) General fatigue class

	Low general Fatigue		Increased general fatigue with mild offset		Severe general fatigue	
Variable	OR	*p*	OR	*p*	OR	*p*
Smoking	ns	ns	ns	ns	**3.03**	**.002**
Physical inactivity	ns	ns	ns	ns	**2.96**	**.002**
NYHA-class III/IV	ns	ns	ns	ns	ns	ns
Psychotropics	**0.28**	**.03**	ns	ns	ns	ns
SMWT<300m	**0.42**	**.007**	ns	ns	ns	ns

*Significant levels >0.1 are displayed as ns, i.e. not significant
†Stroke, COPD, peripheral arterial disease, renal insufficiency

Table4. Trajectories of fatigue and CHF prognosis (multivariate)

	(4a) Model including exertion fatigue		
Variable	HR	95%CI	*p*-value
Male sex	1.67	0.85-3.31	.14
Age≥60	**3.23**	**1.26-8.26**	**.01**
Obesity (BMI>30)	0.48	0.23-1.02	.06
Physical inactivity	**0.43**	**0.21-0.85**	**.02**
Diabetes	1.23	0.63-2.37	.55
LVEF<30%	**2.17**	**1.22-3.87**	**.009**
Low exertion fatigue	**0.12**	**0.02-0.93**	**.04**
Mild exertion fatigue	0.59	0.27-1.32	.20
Increased exertion fatigue with mild offset	0.65	0.19-2.21	.49
Increased exertion fatigue with moderate offset	1.03	0.44-2.41	.95
Severe exertion fatigue	**2.59**	**1.09-6.16**	**.03**
	(4b) Model including general fatigue		
Variable	HR	95%CI	*p*-value
Male sex	1.22	0.63-2.36	.55
Age≥60	**3.70**	**1.45-9.47**	**.006**
Obesity (BMI>30)	0.53	0.25-1.15	.11
Physical inactivity	0.56	0.31-1.02	.06
Diabetes	1.26	0.64-2.46	.51
LVEF<30%	**2.20**	**1.24-3.90**	**.007**
Low general fatigue	0.89	0.42-1.89	.75
Increased general fatigue with mild offset	1.71	0.58-5.07	.33
Severe general fatigue	**3.20**	**1.62-6.31**	**.001**

An additional analysis controlling for use of psychotropic medication ($p>0.5$ in both models) did not significantly alter the model results displayed in Table 4. A final analysis showed that when exertion fatigue and general fatigue were entered in the multivariate model simultaneously, both severe exertion fatigue (HR=2.90; 95%CI 1.14-7.36, $p=.03$) and severe general fatigue (HR=3.00; 95%CI 1.47-6.14, $p=.003$) remained significant predictors of mortality. Similar, the protective effect of low exertion fatigue (HR=0.12;

95%CI 0.02-0.99, p=.05) remained significant as well. This result suggests that independently from each other both types of fatigue add to the risk of mortality in CHF.

Figure 3a. Event free survival stratified by exertion fatigue class

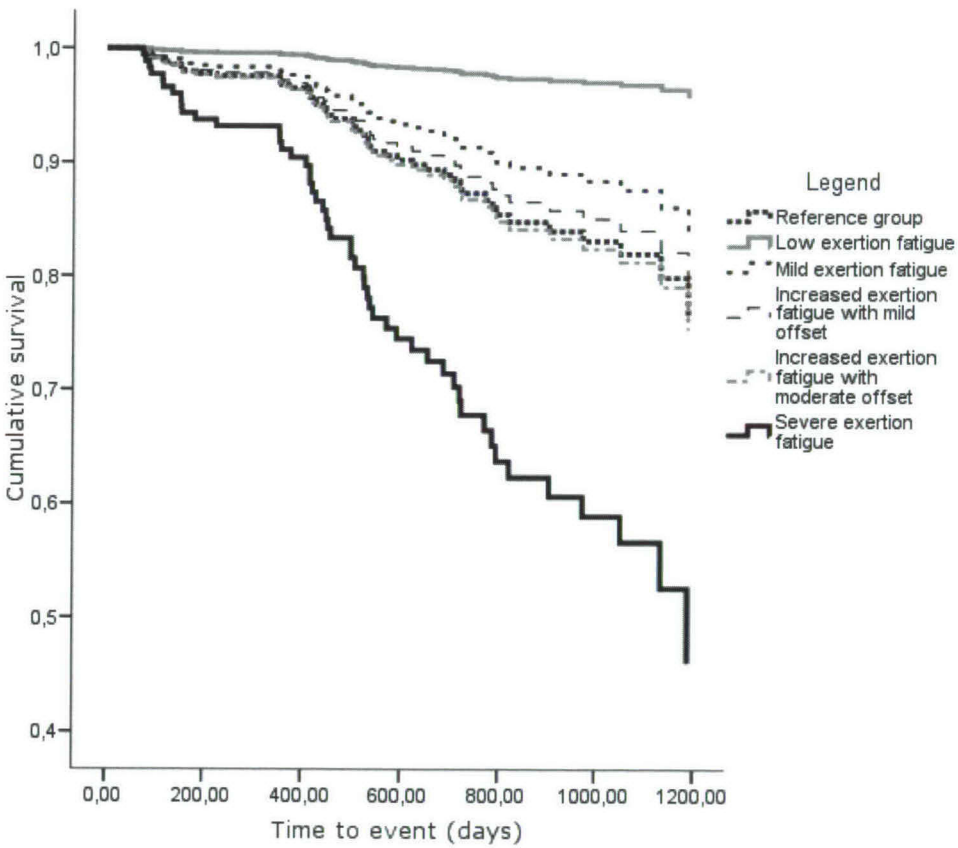
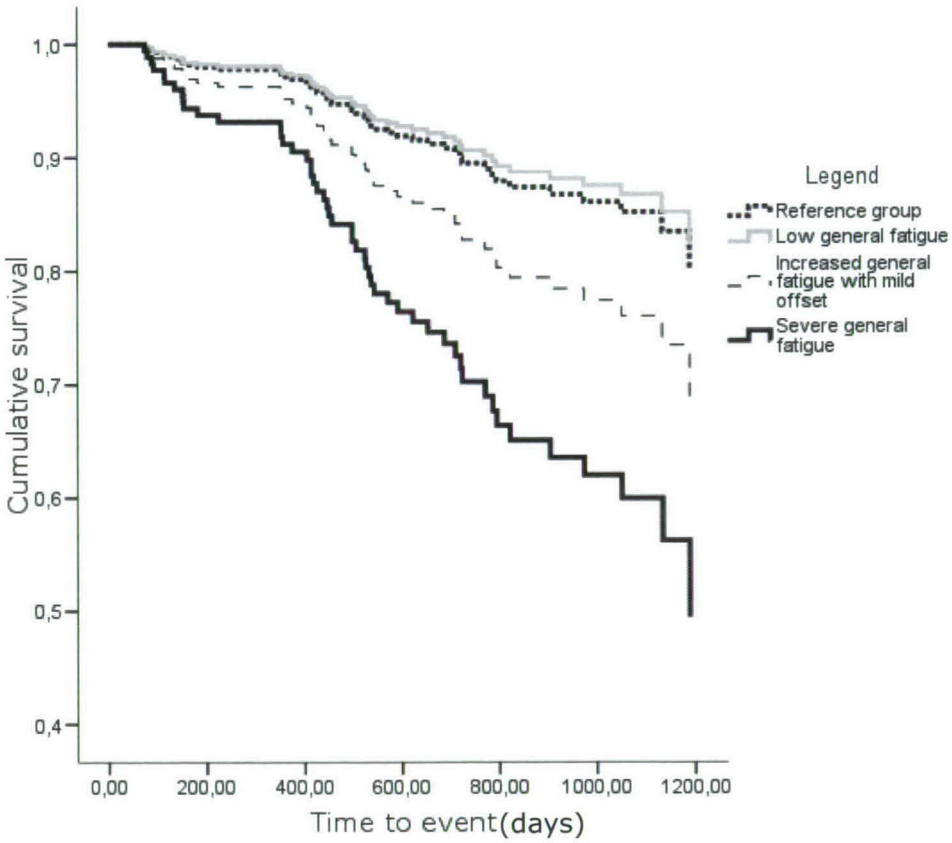


Figure 3b. Event free survival stratified by general fatigue class



DISCUSSION

To our knowledge, this is the first study to examine the course of symptoms of fatigue in patients with CHF. Similar to previous studies (5,12), we differentiated between exertion and general fatigue, and found six distinct trajectories for exertion fatigue and four distinct trajectories for general fatigue. Multinomial logistic regression analysis revealed that sex, age, physical inactivity, diabetes mellitus, comorbidities, NYHA-class, exercise capacity, and psychotropic medication were predictors of exertion fatigue, varying according to classes. Predictors of general fatigue, again varying according to classes, comprised smoking, physical inactivity, and exercise capacity. Cox regression

showed that patients in the severe exertion fatigue class, and severe general fatigue class independently had an almost three-fold increased risk for mortality as compared to the reference group. Patients in the low exertion fatigue group had a decreased risk for mortality.

Fatigue is considered as one of the most important symptoms affecting patients' quality of life. However, fatigue remains under recognized in clinical practice (24,25), as well as an unresolved issue in CHF (12). In the current study, we were able to further refine our understanding of the course of fatigue in CHF, and to characterize most of the trajectories by means of baseline variables. Overall, patients with low/mild levels of exertion/general fatigue were characterized by relative good physical health (no diabetes mellitus, no comorbidities, no physical inactivity, good exercise capacity) and psychological health (no psychotropic medication), whereas the opposite was true for patients with high levels of fatigue. Age and gender effects were found for exertion fatigue. However, we were unable to describe the trajectories that showed an increase of fatigue over time (increased exertion fatigue with mild offset, increased exertion fatigue with moderate offset, and increased general fatigue with mild offset). An explanation for this could be 1) that the groups were relatively small and therefore lacked statistical power to reveal significant differences, and 2) that the overall response levels of fatigue in these trajectories were more similar to the reference group as compared to the more extreme groups, resulting in smaller differences with respect to baseline variables.

From a clinical point of view, knowledge about factors characterizing trajectories that display changes in fatigue over time is important as they point to targets for intervention. Importantly, the findings of the present study indicate that fatigue trajectories are differently related to an increase or decrease in mortality rate. This finding provides further fuel to the 'debate' whether the experience of fatigue is an important factor in itself or merely an unwelcome byproduct of disease progression (26). In previous studies, we have shown that fatigue was associated with rehospitalization (2) and with the combined endpoint of rehospitalization and death (5). A problem with rehospitalization as an outcome measure is its semi-objective nature since the decision to rehospitalize is not solely based on objective diagnostic measures

but also on symptom presentation and symptom interpretation. Therefore, it is important to note that, in the present study, both exertion and general fatigue independently predicted mortality in CHF, above and beyond disease severity and other clinical risk factors. Large-scale studies should give a more in-depth insight into the differential effect of the fatigue trajectories on mortality.

The mechanisms through which fatigue may exert its effect on mortality are unclear. Future studies should assess physiological measures that are known to be abnormal in CHF patients and that are relevant with respect to fatigue, for example measures of abnormal muscle metabolism and an enhanced ergo reflex response (6,7), but also inflammatory markers may be an interesting avenue for research in this regard (27,28). Increased fatigue may also have impact on the patient's ability for self-care, which has been associated with poor prognosis in CHF (29).

The results of the present study advocates the use of a latent growth mixture modeling approach in clinical cardiology research because it allows for the identification of subgroups with distinct developmental patterns. As such, this approach provides additional information beyond that from studying prevalence rates or change scores. A latent class approach has also been used in previous studies (14,22,23,30,31), however without the inclusion of a random intercept. Similar to our studies, these studies also found support for multiple rather than single trajectories, although they examined depressive symptoms (14,22,30), anxiety (23), and quality of life (31), but not fatigue.

This study has a number of limitations. First, the cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern might have influenced patient selection. Second, the examined predictors of the fatigue trajectories were only assessed once. Nevertheless, the strengths of the current study were the repeated assessment of fatigue over time, the prospective design examining the course of fatigue over time using a state-of-the-art modeling approach, and the use of an objective medical outcome. Finally, we used reliable and valid measures of both exertion and general fatigue.

In summary, we found six distinct trajectories for exertion fatigue, and four distinct trajectories for general fatigue in patients with CHF. Several predictors, varying according to classes, could be identified with age, sex,

physical inactivity, comorbidities, exercise capacity, and psychotropic medication use being the most prominent ones. Severe exertion fatigue and severe general fatigue independently predicted an increased mortality risk beyond 12-month follow-up, whereas low exertion fatigue was associated with a decreased mortality risk. Future studies are warranted to confirm these findings, given that this was the first study to examine the course of fatigue in CHF patients. The results of the present study may help identify distinct groups of patients with potentially differential risks of adverse health outcomes, guide future interventions, and therefore be valuable for both research and clinical practice.

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CHAPTER 9:

Somatic/affective depression predicts mortality in chronic heart failure: Can this be explained by co-varying symptoms of fatigue?

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Submitted for publication

ABSTRACT

Aim: We previously showed that somatic/affective symptoms of depression predict mortality in chronic heart failure (CHF), but symptoms of fatigue that are common to both conditions may confound this association. We therefore examined whether fatigue can explain away the relationship between somatic/affective depression and increased risk of mortality in CHF patients. **Methods:** At baseline, 380 consecutive CHF patients were assessed for symptoms of depression, exertion fatigue and general fatigue. Demographic and clinical data were obtained from the patients' medical records or treating cardiologist. The primary endpoint was mortality after a mean follow-up of 2.3 years (SD=1 year). **Results:** At follow-up, 63 patients (16.6%) had died. Exertion fatigue (HR=1.04; 95%CI 1.01-1.06, p=.003), but not general fatigue, was associated with an increased risk of mortality in CHF. Multivariate Cox regression analysis revealed that somatic/affective symptoms of depression (HR=1.09; 95%CI 1.002-1.19, p=.04) were independently associated with increased mortality risk, and that this association could not be explained by exertion fatigue (HR=1.02; 95%CI 0.99-1.05, p=.23). **Conclusion:** The adverse effect of somatic/affective depression on prognosis in CHF was not confounded by exertion fatigue. Behavioral interventions should not only focus on fatigue but also on other somatic/affective manifestations of depression in patients with CHF.

INTRODUCTION

Depression and depressive symptoms have been related to increased mortality in patients with chronic heart failure (CHF) (1-3). Recently, it was shown that the relation between depression and outcome in cardiac disease may be explained by the somatic/affective symptoms of depression, rather than cognitive/affective symptoms of depression (4-8), suggesting that it is important to take into account the differential effect of cognitive/affective and somatic/affective symptoms of depression.

Symptoms of fatigue are highly prevalent among CHF patients (9), and are often considered as one of the key symptoms affecting quality of life (10). In addition, fatigue has been associated with poor outcome in CHF (11-13). In post-myocardial infarction patients, it has been suggested that an explanation for the association between depression and poor outcome may be co-existing symptoms of fatigue (14), as fatigue/energy loss is one of the core characteristics of the somatic/affective domain of depression (15).

However, to the best of our knowledge, this has never been examined in the context of CHF. Therefore, the aim of the present study was to examine whether fatigue may explain away the relationship between somatic/affective symptoms of depression and poor prognosis in patients with CHF.

METHODS

Patients

The sample included 380 consecutive CHF patients, with systolic heart failure and a left ventricular ejection fraction (LVEF) ≤40%, visiting the heart failure outpatient clinic of the TweeSteden Hospital, Tilburg, the Netherlands. Patients with diastolic heart failure (i.e., those with an intact pump function during systole, and diminished filling capacity during diastole), age ≥80 years, myocardial infarction in the month prior to inclusion, other life-threatening comorbidities (e.g., chemotherapy treated cancer), and no or insufficient understanding of spoken and written Dutch language were excluded. All 380 patients completed a questionnaire at baseline. The study protocol was approved by the local medical ethics committee in Tilburg, the Netherlands. The study was conducted conform to the Helsinki Declaration and every patient provided written informed consent.

The majority of subjects was male, married, non-smokers, and not academically educated (Table 1). About half the sample was classified as NYHA-class III/IV, had a cardiac history, had comorbidities, and ischemic CHF. Only a minority of the sample were overweight or anemic. Diuretics, ACE-inhibitors, and beta-blockers were the most prescribed medications.

Demographic and clinical variables

Demographic variables included sex, age, educational level, and marital status. Clinical variables comprised LVEF, NYHA class, etiology of CHF, diabetes, cardiac history (i.e. MI, PCI, CABG), smoking status, BMI, comorbidity (i.e. stroke, COPD, hypertension, peripheral arterial disease, renal insufficiency), and cardiac medication. Information on clinical variables was obtained from the medical records and from the treating cardiologist.

Somatic/affective symptoms of depression

Symptoms of depression were measured by means of the Beck Depression Inventory (BDI) (16). Each item is rated on a 0-3 scale; a total score is obtained by summing together all the items. The BDI is a reliable and well-validated measure of depressive symptomatology (17), and is the most widely used self-report measure of depression (18). The *somatic/affective* domain score (16) was calculated by summing together BDI items 14–21, and comprises symptoms that refer to somatic manifestations of depression (e.g., weight changes, sleep problems). The remaining items refer to cognitive/affective manifestations of depression (e.g., sadness, guilt).

Symptoms of fatigue

Previous research suggest to differentiate between exertion and general fatigue (19); the former referring to fatigue directly related to the performing of activities in daily living, and the latter to an overwhelming, sustained sense of exhaustion that does not necessarily have a relationship with exertion. The Dutch Exertion Fatigue Scale (DEFS) assesses exertion fatigue by means of nine items (20). Items are answered with five response alternatives ranging from 0 (no) to 4 (yes) with total scores ranging from 0 to 36. Chronbach's alpha is high (α=91). The Fatigue Assessment Scale (FAS) was

used to assess symptoms of general fatigue (21), and consists of 10 items, all answered on a 5-point Likert scale, ranging from 0 (never) to 4 (always). A total score is calculated by adding all items, with total scores ranging from 0 to 40. The questionnaire has good internal validity and the reliability of this instrument is high (α=.90).

Clinical endpoints

The primary endpoint in this study was all-cause mortality. Information on mortality (date and cause of death) was collected by checking the hospital's electronic system/the patients' medical records or by contacting the GP.

Statistical analyses

Prior to further statistical analyses, NYHA class, etiology of heart failure, and cardiac history were recoded into dichotomous variables. Discrete variables were compared with the chi-square test and continuous variables with Student's t test for independent samples. Pearson correlations were calculated to evaluate the relations between depression and fatigue. Cox regression analyses was used to examine the impact of somatic/affective symptoms of depression on all-cause mortality while controlling for fatigue. Given the number of fatal events, a maximum of five additional, well-established risk factors was selected a priori in order to obtain reliable estimates in multivariate analyses, i.e. sex, age, NYHA class, smoking, and LVEF.

RESULTS

Clinical predictors of mortality

The mean follow-up period was 2.3 years (SD=1 year). During this period, 63 patients (16.6%) had died. Higher age, NYHA-class III/IV, lower LVEF, and longer time since diagnosis were associated with a higher incidence of mortality (Table 1). Male sex, smoking, prescription of diuretics, and no prescription of beta blockers showed a trend towards significance.

Table 1. Baseline characteristics stratified by incidence of fatal events

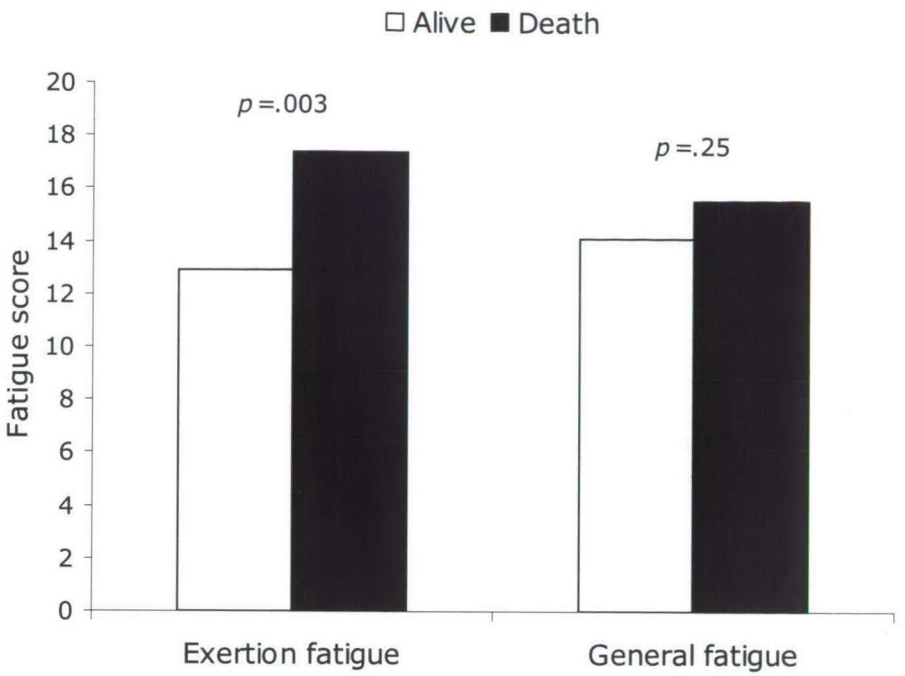
	Total (n=380)	No fatal events (n=317)	Fatal events (n=63)	*p*-value
Demographics				
Age, mean ±SD	65.8 ± 10.4	65.1 ± 10.8	69.1 ± 7.1	<.001
Male sex, % (n)	72.1 (274)	70.3 (223)	81.0 (51)	.09
Having a partner, % (n)	72.1 (274)	72.9 (231)	68.3 (43)	.46
No academic education, % (n)	85.8 (326)	84.9 (269)	90.5 (57)	.24
Disease characteristics				
Ischemic etiology, % (n)	53.9 (205)	53.6 (170)	55.6 (35)	.78
LVEF, Mean ± SD	30.8 ± 6.9	31.4 ± 6.7	27.5 ± 7.1	<.001
NYHA class III/IV, % (n)	39.7 (151)	36.6 (116)	55.6 (35)	.005
Time since diagnosis, yrs ±SD	3.3 (3.9)	3.1 (3.8)	4.3 (4.2)	.03
Cardiac history†, % (n)	57.4 (218)	56.5 (179)	61.9 (39)	.43
Biomedical risk factors				
Smokers, % (n)	23.9 (91)	22.1 (70)	33.3 (21)	.06
BMI, mean ±SD	28.1 ± 5.3	28.2 ± 5.2	27.3 ± 5.8	.19
Comorbidity‡, % (n)	58.2 (221)	56.8 (180)	65.1 (41)	.22
Diabetes, % (n)	24.7 (94)	23.3 (74)	31.7 (20)	.16
Medication				
ACE-inhibitor, % (n)	71.6 (272)	72.6 (230)	66.7 (42)	.34
AT-II antagonists, % (n)	18.4 (70)	17.0 (54)	25.4 (16)	.12
Diuretics, % (n)	72.9 (277)	71.0 (225)	82.5 (52)	.06
Beta blockers, % (n)	67.1 (255)	69.1 (219)	57.1 (36)	.07
Statins, % (n)	51.1 (194)	51.1 (162)	50.8 (32)	.96
Calcium antagonists, % (n)	11.3 (43)	11.4 (36)	11.1 (7)	.96
Aspirin, % (n)	40.8 (155)	41.0 (130)	39.7 (25)	.85
Psychotropics, % (n)	11.6 (44)	12.3 (39)	7.9 (5)	.32

† History of MI, CABG, PCI
‡ Stroke, COPD, hypertension, peripheral arterial disease, renal insufficiency

Association between fatigue and depression

Exertion fatigue and general fatigue were both significantly associated with total depressive symptoms (BDI total score: r=.54, $p<.001$ and r=.66, $p<.001$; respectively), the somatic/affective subscale (r=.62; $p<.001$ resp. r=.65; $p<.001$), and the cognitive/affective subscale (r=.39; $p<.001$ resp. r=.55; $p<.001$) of the BDI. As expected, the association between exertion fatigue and cognitive/affective symptoms of depression was moderate, suggesting exertion fatigue is representing physical aspects of fatigue, whereas general fatigue seems to capture both physical and mental aspects of fatigue.

Figure 1. Mean levels of exertion and general fatigue stratified by survival status



Exertion fatigue, depression and mortality

Cox regression analysis revealed that exertion fatigue was associated with mortality in univariate analysis (HR=1.04; 95%CI 1.01-1.06, p=.003), whereas general fatigue (HR=1.02; 95%CI 0.99-1.05, p=.25) was not. As displayed in figure 1, mean levels of exertion fatigue were significantly higher in patients that died. After adjusting for sex, age, NYHA class, smoking, and LVEF, exertion fatigue (HR=1.04; 95%CI 1.01-1.06, p=.003) remained a significant predictor of mortality in CHF. As reported previously, patients high on somatic/affective depression symptoms also had a significantly increased mortality risk compared to non-depressed patients (5-7).

To determine whether the effect of somatic/affective symptoms of depression on mortality can be explained by exertion fatigue, we added exertion fatigue to the multivariate model including the somatic/affective depression domain score, sex, age, NYHA class, smoking, and LVEF. Cox

regression analysis revealed that adding exertion fatigue (HR=1.02; 95%CI 0.99-1.05, p=.23) did not significantly alter the effect of somatic/affective symptoms of depression (HR=1.09; 95%CI 1.002-1.19, p=.04) on mortality (Table 2).

Table 2. Predictors of mortality in CHF (multivariate)

	HR	95%CI	p-value
Male sex	1.45	0.75-2.78	.27
Age	1.04	1.01-1.07	.006
Smoking	1.79	1.03-3.11	.04
NYHA-class III/IV	1.10	0.63-1.90	.74
LVEF	0.94	0.91-0.98	.002
Exertion fatigue	1.02	0.99-1.05	.23
Somatic/affective symptoms of depression	1.09	1.01-1.19	.04

DISCUSSION

The present findings suggest that the effect of somatic/affective symptoms of depression on mortality risk in patients with CHF cannot be explained away by co-varying symptoms of fatigue. Hence, this provides further evidence for the notion that somatic/affective symptoms of depression should be examined in their own right in relation to cardiovascular prognosis. Lately, it has become apparent that depression in cardiovascular disease is atypical (22), and that the prognostic value for hard medical outcomes of the cognitive/affective dimension of depression is less evident than that for somatic/affective symptoms (4,6-8). Depressed mood, however, does remain relevant and important in cardiovascular disease, in particular in terms of affecting the patients' quality of life (23).

Apart from depression, it was shown that exertion fatigue, but not general fatigue, predicted mortality in CHF. Previously, it was demonstrated that exertion fatigue was primarily determined by physical aspects of CHF such as hypertension, and exercise capacity (19), suggesting that exertion fatigue reflects the direct physical consequences of the disease itself. The current study showed that exertion fatigue was a predictor of mortality in CHF

independent from reduced cardiac output. Hence, the origin of exertion fatigue may lie elsewhere. Two recent reviews suggest that skeletal muscle abnormalities in CHF might be responsible for the sensation of fatigue (24,25), which in turn could be a result of a combination of disuse, impaired perfusion, and catabolic myopathy (25). Future studies should examine whether exertion fatigue relates to these factors.

Exertion fatigue did not explain the association between somatic/affective symptoms of depression and mortality in CHF suggesting that a broader array of somatic symptoms is important in predicting CHF mortality. In line with what was discussed for exertion fatigue, somatic/affective symptoms of depression (e.g. fatigue, loss of appetite, loss of sexual pleasure) might reflect several underlying physiological processes that are not generally accounted for in standard prognostic models. Immune factors are important in this regard, because they are known to predict poor outcome in CHF (26-29) and have also been associated with depressive symptoms (30,31). It would therefore be interesting to examine the predictive value of somatic/affective symptoms while controlling for immune factors. However, it is also possible that somatic/affective symptoms reflect distinct manifestations of depression that are perceived by cardiac patients to be more relevant to describe their mental health status (32) as compared to the more obvious cognitive symptoms of depression (22).

The findings of the present study have important implications for treatment of fatigue and depression in CHF. Previous work has shown that exercise training reduces autonomic derangement, neurohumoral activation, and symptoms of fatigue and dyspnoea (33,34), and would therefore be a viable option for treatment of fatigue in CHF. However, the findings of the present study suggest that additional behavioral interventions may be needed to reduce the risk associated with other somatic/affective manifestations of depression. Importantly, recent research indicates that somatic/affective symptoms of depression are often overlooked in cardiac patients; as a result, depression is recognized in fewer than 1 in 3 cardiac patients (8). Our findings thus also call for a greater awareness of somatic/affective symptoms of depression in CHF patients.

A number of limitations should be mentioned. The follow-up period was relatively short. Furthermore, the sample could be biased by mobility and younger age, because participating patients were required to visit the outpatient clinic. Finally, the sample used in this study was quite heterogeneous, as end stage CHF patients as well as newly diagnosed CHF patients were included. However, this is also a strength, as it reflects "the real world" of CHF patients seen in daily clinical practice. Other strengths of the study include the use of valid and reliable questionnaires to assess symptoms of fatigue, and that this is the first study to examine the prognostic value of fatigue and somatic symptoms of depression together in patients with established CHF.

In summary, somatic/affective symptoms of depression predicted mortality in CHF, and this effect was not confounded by exertion fatigue. These findings indicate that clinicians should be aware of somatic/affective symptoms of depression, and that behavioral interventions should not only focus on fatigue but also on other somatic manifestations of depression in patients with CHF.

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CHAPTER 10:

General summary and discussion

This thesis presents the results of several studies examining the role of psychological factors in chronic heart failure (CHF). In this chapter, the main findings are presented and implications for research and clinical practice are discussed.

Vital exhaustion in chronic heart failure

Previous studies have examined the role of vital exhaustion in coronary artery disease (CAD). It has been shown that vital exhaustion predicts new onset of coronary events (1,2) as well as recurrent coronary events (3,4). Furthermore, vital exhaustion has been linked to a range of physiological parameters that could potentially explain the association between vital exhaustion and adverse outcome in CAD (5-19). However, an intervention study aimed to reduce vital exhaustion in percutaneous coronary intervention (PCI) patients did not improve prognosis, suggesting that vital exhaustion is not part of a causal chain but merely a reflection of ongoing physiological processes (20). Vital exhaustion has not been studied previously in CHF.

The first part of this thesis covered several aspects of the relationship between vital exhaustion and CHF and aimed to examine the nature and course of vital exhaustion in CHF, as well as the interrelationships between vital exhaustion and disease stage within CAD and other prevalent and influential psychological factors.

In chapter 2, the nature of vital exhaustion in CHF was investigated. Principal component analysis revealed four essential features which are, in order of importance, fatigue, cognitive-affective symptoms of depression, sleep problems, and lack of concentration. This result was in line with a previous study in MI patients (21). The components of vital exhaustion show considerable similarity to symptom dimensions found in major depression. However, their emphasis is different. In vital exhaustion, the starting point is a state of unusual tiredness (1) which is often accompanied by cognitive-affective depressive symptoms, sleep problems, and lack of concentration, whereas the core symptoms of depression are low mood and loss of interest that often go together with fatigue, sleep problems, and loss of appetite (22). The study presented in chapter 2 supports this notion by showing that 1) fatigue explains more of the variance in vital exhaustion as compared to the

other subcomponents, and 2) low mood and loss of interest are not explicitly part of the cognitive-affective depressive symptoms component of the Maastricht Questionnaire that assesses vital exhaustion. All in all, this part of the study indicates that in spite of previous statements (23), vital exhaustion and depression are not simply interchangeable.

Subsequently in chapter 2, the individual components of vital exhaustion (fatigue, cognitive-affective symptoms of depression, sleep problems, and lack of concentration) were used to identify distinct profiles of vital exhaustion in CHF patients: a subgroup without vital exhaustion scoring low on all components, a first subgroup with vital exhaustion scoring high on fatigue and lack of concentration, but low on depressive symptoms and sleep problems, and a second subgroup with vital exhaustion scoring high on all components. Both vitally exhausted groups displayed higher levels of impaired health status as compared to the subgroup without symptoms of vital exhaustion. Exhausted patients manifesting all symptoms were more likely to be rehospitalized than patients without vital exhaustion. Vitally exhausted patients without depressive symptoms and sleep problems also showed a tendency for more hospitalizations but this was not statistically significant. These results indicate that focusing on symptoms of depression alone may not be sufficient, since patients with elevated levels of fatigue and lack of concentration, but with a relative absence of depressive symptoms and sleep difficulties, also had impaired health status, and showed a tendency towards an increased risk for rehospitalization. Focusing on clusters of psychological risk factors rather than a single risk factor has been advocated by others as a more detailed examination of symptom profiles may lead to better informed development of more effectively timed and more specifically tailored behavioral interventions (24,25). This "subclinical" group may therefore be a relevant target for future interventions, which corresponds to findings from an earlier profile study in MI patients (26).

In chapter 3, the main components of vital exhaustion, fatigue and depressive symptoms were used as outcome measures at 12-month follow-up in a combined sample of CHF and PCI patients. The results indicated that ischemic heart disease stage was not associated with the core symptoms of vital exhaustion. In other words, CHF patients did not report more symptoms of

fatigue and depression as compared to PCI patients. In contrast, Type D personality did predict symptoms of vital exhaustion at 12-month follow-up, and this effect was not moderated by ischemic heart disease stage. Although it may seem counterintuitive that a more severe disease stage is not associated with more symptoms of fatigue and depression, this result may indicate that the physiological course of a disease is not necessarily on par with the psychological course. CHF patients often have a longer and more severe cardiac history as compared to PCI patients. Therefore, they may be better accustomed to the disease, which in turn could mask the objectively increased physical deterioration. More importantly, this study revealed that symptom perception is, at least partly, dependent on psychological factors. This knowledge could potentially be very relevant for clinicians and other health care professionals when evaluating the patient's symptom presentation.

Chapter 4 focused on the course of vital exhaustion in a combined sample of MI and CHF patients over a 12 month period. The results supported the existence of multiple trajectories rather than one. Latent class mixture modeling revealed four different trajectories of vital exhaustion: low vital exhaustion, decreasing vital exhaustion, increasing vital exhaustion, and severe vital exhaustion. It turned out that the majority of patients displayed stable patterns of vital exhaustion over time, which is line with findings from previous studies examining the trajectories of depression (27-29), and anxiety (30).

Furthermore, a marked difference was found between sample group (MI vs. CHF) and trajectory group membership. MI patients were more likely to be in the increasing vital exhaustion group, whereas CHF patients were more likely to be in the severe vital exhaustion group. Remarkably, almost half of the total CHF sample was found in the stable severe vital exhaustion group. In both the increasing and severe vital exhaustion groups, the likelihood of cardiovascular events was higher as compared to the low vital exhaustion group. These findings suggest that a significant number of patients after a MI do not fully recover but deteriorate over time, and may represent a group of MI patients that do not respond to standard treatment procedures, which is in line with studies that have shown that persistence of depressive symptoms, despite

treatment, predicts increased cardiac risk (28,31,32). In addition, most vulnerable MI and CHF patients may differ in their patterns of vital exhaustion.

Overall, the findings of the first part of this thesis provide evidence for the relevance of vital exhaustion in the context of CHF. First of all, it was shown that vital exhaustion is a broader concept than fatigue, and that it is not interchangeable with depressive symptoms. Second, profile analysis demonstrated the relevance of subclinical presentation of symptoms of vital exhaustion, primarily expressed as fatigue in absence of depressive symptoms. Third, a large proportion of CHF patients displayed stable patterns of vital exhaustion. Close to half of the CHF sample was found to have stable and severe levels of vital exhaustion over time, and were at increased risk for adverse cardiac events. This indicates that, despite improved treatment modalities, a significant part of the CHF population does not improve over time in terms of vital exhaustion, and suggests that other modes of intervention are imperative.

Symptoms of fatigue in chronic heart failure

So far, fatigue has received little attention in the HF literature, even though fatigue is often rated as one of the most disabling symptoms in CHF (33). Previous studies have underlined the importance of symptoms in CHF, both in terms of prognosis (34,35) and health status (36). Several unknown aspects of fatigue in CHF were addressed in this thesis among which were explaining individual differences in fatigue, investigating the course of fatigue over time, and the interrelationship with coexisting symptoms of depression and their impact on prognosis.

As suggested by previous studies, different types of fatigue can be distinguished in CHF (37). In chapter 5, exertion fatigue and general fatigue were identified as distinct types of fatigue. Exertion fatigue is directly related to the performing of activities in daily living, whereas general fatigue reflects an overwhelming, sustained sense of fatigue that does not necessarily have a relationship with exertion. Although both types of fatigue are not mutually exclusive, it is still important to distinguish between them because the origin and relevance of exertion and general fatigue in CHF might be different, which in turn may help to guide future (tailored) interventions. This is illustrated by

the second part of chapter 5, in which it was shown that exertion fatigue was primarily predicted by physical characteristics, whereas general fatigue was predicted by both physical and psychological characteristics. Exertion fatigue may therefore primarily be of peripheral origin, resulting from neuromuscular dysfunction outside the central nervous system, and may therefore relate to impaired neurotransmission in peripheral nerves and/or defects in muscular contraction. The latter processes have been observed in CHF as well (38,39). General fatigue might be more closely related to fatigue at a central level, and implies alterations or abnormalities in neurotransmitter pathways within the central nervous system, and often co-exists with psychological co-morbidities (40,41).

Fatigue is common in other conditions as well. A substantial proportion of patients who have had a stroke perceive fatigue as their worst or one of their worst symptoms (42). Results of chapter 6 indicated that the Fatigue Assessment Scale, as a measure of general fatigue, has good psychometric properties in stroke patients. Furthermore, it was found that the levels of general fatigue were similar in stroke patients and CHF patients but were considerably higher compared to healthy controls, emphasizing its clinical significance in CHF and stroke.

Levels of fatigue can change over time, but the dynamic nature of fatigue has not been studied in the context of CHF thus far. In the study presented in chapter 7, exertion fatigue and general fatigue were measured at baseline and 12-month follow-up, and changes over time were linked to the combined clinical endpoint cardiac re-admission or death beyond 12-months follow-up. It was demonstrated that changes in exertion fatigue, but not general fatigue, predicted adverse events beyond 12-months follow-up. Two important lessons can be learned from this study. First, within-subject changes of fatigue are clinically relevant, and patients that display an increase in symptoms of fatigue should be taken seriously as they have an increased risk for adverse events. Second, changes in exertion fatigue might be more relevant in the context of CHF as compared to changes in general fatigue as they may indicate worsening of heart failure.

Other than studying changes in fatigue within a total group, modern statistical techniques allow for the identification of classes of individuals, who

follow similar behavioral patterns over time. In chapter 8, it was shown that for both exertion fatigue and general fatigue multiple trajectories could be distinguished. The majority of patients displayed stable trajectories over time, and it was shown that patients in both the severe exertion fatigue and the severe general fatigue group had an increased risk for mortality. In contrast to the study presented in chapter 7, general fatigue did predict poor outcome in CHF, which can most likely be explained by the use of different study designs, i.e. in chapter 7 changes in fatigue were studied, whereas the aim of chapter 8 was to identify distinct trajectories of fatigue over time. The results indicated that changes over time occurred less frequent in general fatigue as compared to exertion fatigue, reducing its power to predict adverse events. The results of chapter 8 demonstrate that high baseline levels of both exertion and general fatigue are not likely to decrease over time, despite optimal pharmacological treatment, and that these groups are at increased risk for mortality.

Fatigue and depression often co-exist in patients with cardiovascular disease (43). A recent study showed that the relation between depression and outcome in CHF may be explained by the somatic/affective symptoms of depression, rather than cognitive/affective symptoms of depression (44). It has previously been suggested that an explanation for the association between depression and poor outcome may be co-existing symptoms of fatigue (45). However, the results of the study reported in chapter 9 do not support this hypothesis. It was shown that somatic/affective symptoms of depression were independently associated with increased mortality risk and that this association could not be explained by exertion fatigue and general fatigue. This suggests that a broader array of somatic/affective symptoms is important in predicting CHF mortality. The somatic/affective symptoms of depression might reflect several underlying physiological processes that are not generally accounted for in standard prognostic models. It would be interesting to examine the predictive value of somatic/affective symptoms while controlling for immune factors since they are known to predict poor outcome in CHF (46), and have also been associated with depressive symptoms (47,48). It has also been suggested that somatic/affective symptoms of depression reflect distinct manifestations of depression that are perceived by cardiac patients to be more relevant to describe their mental health status (49). There is however little

empirical support for this point of view, and clinical trials aimed to reduce depression by psychosocial interventions or antidepressant treatment in CAD patients have not been able to prolong survival (50-52), despite effective treatment of depression (50,51).

Of note, before taking somatic/affective symptoms into account, exertion fatigue, but not general fatigue, both measured at baseline, predicted mortality in CHF. Taking into account the results from the previous chapters, exertion fatigue seems a more consistent predictor of adverse outcomes in CHF as compared to general fatigue. Exertion fatigue might primarily reflect the direct consequences of CHF, and may therefore be a more relevant measure for CHF patients in terms of predicting prognosis. In contrast, general fatigue has a more ambiguous nature, and might not be specific enough in this regard.

All in all, the results of part B of the present thesis indicate that fatigue is an important factor in CHF. It was shown that two types of fatigue should be distinguished in CHF, i.e. exertion fatigue and general fatigue. Exertion fatigue seems most relevant in terms of predicting prognosis, and can potentially be used for risk stratification in CHF. However, exertion fatigue did not tell the whole story. It seems that a broader array of somatic/affective symptoms of depression should be taken into account when predicting adverse outcomes in CHF.

Implications for research and clinical practice

Vital exhaustion

Until now, vital exhaustion had primarily been studied in CAD patients. Vital exhaustion was shown to predict adverse outcome in this patient group, and to be associated with a range of physiological parameters, but a behavioral intervention aimed to reduce vital exhaustion did not lead to improved prognosis (53). The studies presented in this thesis showed that vital exhaustion is also an important risk marker in CHF (Chapter 3 & 4). However, more research is needed to determine whether vital exhaustion can also qualify as a modifiable risk factor that is a determinant that can be modified by an intervention and reduce the probability of adverse outcomes. Several research questions remain unanswered, the most important one being the extent to which vital exhaustion is the result of behavior as opposed to physiological

processes related to CHF. It seems much more plausible that vital exhaustion can be the result of overextending oneself within a middle-aged working population without a cardiac history. In contrast, CHF patients have to deal with a serious condition that is often accompanied by an extensive cardiac history and other burdensome comorbidities. Hence, vital exhaustion as a modifiable risk factor seems less relevant in the context of CHF. Future studies should examine this.

More research is also needed to explain vital exhaustion in CHF. Studies in chapter 2 & 3 identified demographic, clinical, and psychological associates of vital exhaustion. Future studies should include physiological measures that are known to be abnormal in CHF patients and that are relevant with respect to vital exhaustion, for example measures of abnormal muscle metabolism, an enhanced ergo reflex response, and increased levels of pro-inflammatory markers (38,39,54).

Cluster analysis revealed a subclinical group with elevated levels of fatigue and lack of concentration, but with a relative absence of depressive symptoms and sleep problems (Chapter 2). Evidence was found that these patients generally have poor health status, and have a tendency towards more hospitalizations. However, large-scale studies with hard medical endpoints are required to obtain a more in-depth insight into the clinical relevance of this group.

In chapter 4, different trajectories of vital exhaustion were identified and their subsequent impact on prognosis. In this chapter, total scores of vital exhaustion were used, but as was shown in chapter 2, vital exhaustion comprises four different dimensions. It would be interesting to do a separate trajectory analysis for each component, and to determine what component turns out to be the most prominent predictor of adverse outcomes in CHF. Identifying the most cardio-toxic components of vital exhaustion may help to develop future interventions.

In clinical practice, recognizing symptoms of vital exhaustion is important since they are a risk marker for poor prognosis. Information on daily activities and engagement in physical exercise may guide intervention. Recently, it has been shown that CHF patients may benefit from physical exercise programs with a good balance between resting and activity being an

important factor (55). Since the perception of vital exhaustion may also depend on co-morbid depression, anxiety, and/or personality factors, referral to a clinical psychologist should be set at a low threshold.

Symptoms of fatigue

Even though the present thesis identified several predictors of fatigue, and showed that fatigue is a risk marker for adverse events in CHF, it is still a poorly understood symptom, especially from a physiological point of view. Similar to vital exhaustion, studies are needed to test the associations between the subjective experience of fatigue and relevant parameters in CHF, like enhanced ergo reflex response, and increased levels of pro-inflammatory markers (38,39,54).

Latent class analysis revealed multiple trajectories of exertion fatigue and general fatigue. Although associations were found between mortality and the more extreme (stable) groups, no associations were found with trajectories that displayed changes in fatigue over time. The trajectories that displayed change were generally small groups of patients, and usually lacked power to confirm an association with mortality. In chapter 4, the increasing vital exhaustion trajectory did in fact predict adverse events in CHF, but the sample of this study was twice as big as compared to the trajectory analysis on exertion and general fatigue. Hence, larger samples are required to determine whether trajectories of exertion and general fatigue, that display changes over time, are clinically significant.

Future interventions should focus on decreasing fatigue in CHF as recommended by the European Society of Cardiology (56). Symptom relief is also one of the most important targets of care and treatment for the patients themselves (57,58). Venues for interventions could be exercise training, support groups, or cognitive behavioural therapy (20,55,59,60).

In order to provide optimal treatment, some patients may need more intensive follow-up as compared to others. The present thesis suggests that especially those patients with severe exertion fatigue (chapter 8) or increasing exertion fatigue over time (chapter 7) are at increased risk for adverse events. In addition to cardiologists and general practitioners, other health care

professionals such as nurse practitioners and psychologists might potentially contribute to better care and management of CHF patients.

Limitations and strengths of the thesis

The present thesis had some limitations. First, there may have been bias in the selection of patients. The cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern may have influenced selection. For example, patients that go along well with their doctor may more easily have agreed to participate.

Second, all CHF data were collected in the same hospital. This could make generalizations of the results difficult. Multi-centre studies are needed to confirm our findings in the CHF population at large.

Third, psychological variables were assessed by means of questionnaires. It has been shown that measurement by questionnaires is not very accurate (61). Response errors can be due to poor memory, poor comprehension, personal norms and values, and social desirability (61,62). In a recent study, a response set without questions was administered to a sample of students together with two personality questionnaires. Surprisingly, it was found that positive answers were associated with low neuroticism, high extraversion, and high well-being (63). The results of this study potentially question the validity of some of the associations found in this thesis. For example, the associations between Type D personality and symptoms of fatigue and depression reported in chapter 2. Perhaps, these associations are partly the result of a general tendency towards positive or negative response categories. This notion is also important when psychological factors are used as predictors of hard medical outcomes. How valid are our measures on a conceptual level? Do we really measure fatigue, depression, or personality as distinct concepts? Perhaps it is the shared variance between psychological measures that explains the association with adverse outcomes.

On the other hand, this thesis also had a number of strengths. First, the repeated assessment of vital exhaustion and fatigue over time and the prospective design that was used in most chapters provided the opportunity to not only study between-subject variance, but also within-subject variance.

Second, the use of advanced statistical techniques gave us more detailed information. Chapter 4 and 8 applied latent class mixture modeling which allows for the identification of distinct groups of patients following a similar behavioral pattern over time. This method provided us with some interesting subgroups of CHF patients with differential risks for health outcomes. A related method was used in Chapter 2, latent class cluster analysis, which was used to identify profiles of vital exhaustion. Latent class cluster analysis is preferred over traditional cluster analysis because the cluster criterion is less arbitrary, no decision on the scaling of observed variables has to be made, and there are more formal criteria on which to base decisions on the number of clusters.

Concluding remarks

Fatigue and vital exhaustion are important but neglected issues in CHF. Severe and persistent vital exhaustion, exertion fatigue, and general fatigue were present in a significant proportion of patients with CHF. It was shown that psychological factors (e.g. Type D personality, depressive symptoms) influenced the perception of symptoms of general fatigue and vital exhaustion, and should be taken into account when health care professionals evaluate the patient's symptom presentation. Exertion fatigue was less dependent on psychological factors. Future studies should examine the associations between fatigue, vital exhaustion, and relevant physiological parameters to determine the extent to which the subjective experience of these symptoms reflect disease related and/or psychological processes. This information is vital to help guide future interventions aimed to reduce symptoms in CHF.

Vital exhaustion and exertion fatigue turned out to be powerful predictors of adverse outcomes in CHF. Inconsistent results were found for general fatigue in this regard, and can be used to identify high-risk patients. These patients should be provided with more intense follow-up to improve their symptom levels, and potentially prolong their survival. Future studies are needed to develop effective treatment modalities to achieve this.

Overall, it can be concluded that there is an urgent need to understand symptoms in CHF. The findings from the present thesis clearly demonstrate the importance of fatigue and vital exhaustion in this context.

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Nederlandse samenvatting (Dutch summary)

De prevalentie van chronisch hartfalen neemt vandaag de dag epidemische vormen aan. De belangrijkste oorzaken hiervan zijn het toenemend aantal ouderen, en verbeterde behandelingsmogelijkheden na een hartinfarct. Kenmerkend voor deze patiëntengroep is een slechte tot matige pompfunctie van het hart. In veel gevallen leidt dit tot klachten van kortademigheid en vermoeidheid. Onderzoek heeft uitgewezen dat hartfalenpatiënten vermoeidheid ervaren als het meest belastende symptoom van hun ziekte. Wetenschappelijk onderzoek naar de rol van vermoeidheid bij hartfalen vindt echter op zeer beperkte schaal plaats.

In het eerste deel van dit proefschrift is de rol van vitale uitputting bij hartfalen onderzocht. Vital uitputting kan gedefinieerd worden als een toestand gekenmerkt door vermoeidheid, stemmings-, slaap-, en concentratieproblemen. Voorgaand onderzoek heeft aangetoond dat vitale uitputting een belangrijke precursor is van een hartinfarct. In de context van hartfalen is de rol van vital uitputting tot op heden onderbelicht gebleven.

In hoofdstuk 2 is de aard van vitale uitputting bij hartfalen nagegaan. Met behulp van een principale componenten analyse kon de onderliggende structuur van vital uitputting worden onderschreven, namelijk een toestand gekenmerkt door vermoeidheid, stemmings-, slaap-, en concentratieproblemen. Deze factoren zijn vervolgens gebruikt om te komen tot een profilering van vitale uitputting bij hartfalen. Aan de hand van een latente cluster analyse konden drie verschillende profielen van vital uitputting geïdentificeerd worden: een subgroep van patiënten die laag scoorden op alle factoren van vitale uitputting, een subgroep van patiënten die hoog scoorden op alle factoren van vitale uitputting, en een subgroep van patiënten die hoog scoorden op vermoeidheid en concentratieproblemen, maar laag scoorden op stemmings- en slaapproblemen. Vervolgens bleek dat de subgroepen met verhoogde scores op vital uitputting een verminderde gezondheidstoestand hadden, en dat deze subgroepen een verhoogde kans hadden op heropname in het ziekenhuis vanwege hartfalen. De resultaten van hoofdstuk 2 laten zien dat het van belang is om te focussen op clustering van verschillende (psychologische) factoren. Het in ogenschouw nemen van symptoomprofielen zou namelijk kunnen leiden tot meer gerichte en meer efficiënte interventies.

In hoofdstuk 3 is ingegaan op de vraag in hoeverre klachten van vital uitputting bepaald worden door de mate van ischemisch hartlijden ten opzichte van persoonlijkheidskenmerken. Uit de resultaten bleek dat de mate van ischemisch hartlijden geen invloed had op klachten van vital uitputting. Daarentegen bleek dat patiënten met een Type D persoonlijkheid, gekenmerkt door een combinatie van negatieve affectiviteit en sociale inhibitie, een grotere kans hadden op klachten van vitale uitputting ten opzichte van patiënten zonder deze persoonlijkheidskenmerken. Bij de evaluatie van gezondheidsklachten zou daarom ook rekening gehouden moeten worden met de persoonlijkheid van de patiënt.

In hoofdstuk 4 is het verloop van vitale uitputting over een periode van 12 maanden bestudeerd. Aan de hand van een latente klassen mixture modellering werden een viertal verschillende trajecten gevonden: een traject met stabiele, lage scores op vitale uitputting, een traject met toenemende scores op vitale uitputting, een traject met een afnemende scores op vitale uitputting, en een traject met stabiele, hoge scores op vitale uitputting. Bijna de helft van alle hartfalenpatiënten bleek te zitten in de groep met stabiele, hoge scores, ondanks optimale medische behandeling. Verder bleek dat patiënten in deze groep een significant hogere kans hadden op een slechte prognose.

In het tweede deel van dit proefschrift is de rol van inspanningsvermoeidheid en algemene vermoeidheid bij hartfalen onderzocht. Inspanningsvermoeidheid kan gezien worden als vermoeidheid die het directe gevolg is van activiteiten in het dagelijks leven, terwijl algemene vermoeidheid niet direct een relatie met inspanning hoeft te hebben. Ook voor deze vormen van vermoeidheid geldt dat er relatief weinig onderzoek naar is gedaan binnen de context van hartfalen.

In hoofdstuk 5 zijn voorspellers van inspanningsvermoeidheid en algemene vermoeidheid onderzocht. Uit de resultaten bleek dat inspanningsvermoeidheid het beste voorspeld werd door inspanningscapaciteit, kortademigheidsklachten, hypertensie, en depressieve klachten. Daarentegen werd algemene vermoeidheid het beste voorspeld door kortademigheidsklachten, depressieve klachten, Type D persoonlijkheid, en slaapproblemen.

In hoofdstuk 6 is een vergelijking gemaakt tussen algemene vermoeidheidsklachten bij hartfalenpatiënten ten opzichte van herseninfarctpatiënten. Bij herseninfarctpatiënten lijkt vermoeidheid nog een meer genegeerde klacht te zijn dan bij hartfalen. Uit de resultaten van hoofdstuk 6 bleek echter dat het niveau van vermoeidheidsklachten bij hartfalers en herseninfarctpatiënten vergelijkbaar is.

In hoofdstuk 7 is onderzocht in hoeverre verandering van vermoeidheid over tijd voorspellend is voor de prognose op langere termijn. Toename in inspanningsvermoeidheid tussen de baseline en 12 maanden follow-up bleek een significante voorspeller te zijn van een slechte prognose, ook na controle voor standaard risicofactoren zoals roken en diabetes.

In hoofdstuk 8 is het verloop van inspanningsvermoeidheid en algemene vermoeidheid bestudeerd. Aan de hand van een latente klassen mixture modellering werden 6 verschillende trajecten gevonden voor inspanningsvermoeidheid, en 4 verschillende trajecten voor algemene vermoeidheid. Uit vervolganalyses bleek dat patiënten met stabiele en hoge scores op inspanningsvermoeidheid en algemene vermoeidheid een hogere kans hadden op vroegtijdig overlijden in vergelijking met patiënten met gematigde vermoeidheidsscores. Hartfalenpatiënten met stabiele en lage scores op inspanningsvermoeidheid hadden juist een verminderde kans op vroegtijdig overlijden.

Ten slotte is in hoofdstuk 9 de relatie tussen somatisch-affectieve symptomen van depressie, vermoeidheid, en prognose nagegaan. Een recente studie heeft aangetoond dat de relatie tussen depressie en prognose bij hartfalen verklaard wordt door de somatisch-affectieve component van depressie. In dit hoofdstuk is onderzocht of vermoeidheid vervolgens het effect van somatisch-affectieve symptomen van depressie op prognose zou kunnen verklaren. Uit de resultaten bleek echter dat somatisch-affectieve symptomen van depressie voorspellend waren voor een slechte prognose bij hartfalen ook na correctie voor vermoeidheidsklachten.

De resultaten van dit proefschrift laten zien dat persisterende klachten van vitale uitputting, inspanningsvermoeidheid, en algemene vermoeidheid frequent aanwezig zijn bij hartfalenpatiënten. Daarnaast is gebleken dat psychologische factoren zoals depressie en persoonlijkheid invloed hebben op

de symptoomperceptie van patiënten. Clinici zouden hier rekening mee moeten houden bij de evaluatie van klachten die hartfalenpatiënten naar voren brengen. Vitale uitputting en inspanningsvermoeidheid bleken ook krachtige voorspellers te zijn van een slechte prognose bij hartfalen. Patiënten met vermoeidheidsklachten zouden daarom meer intensief opgevolgd moeten worden. Vermindering van vermoeidheidsklachten zou kunnen leiden tot een betere kwaliteit van leven, en mogelijk ook tot een verbeterde prognose. Toekomstig onderzoek zal moeten leiden tot effectieve interventies gericht op het verminderen van vermoeidheidsklachten bij hartfalen om dit te bereiken.

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Robert, Aug. '09
Bergen, Noorwegen

Publications

List of publications

1. Schiffer AA, Denollet J, Widdershoven J, Hendriks EH, & **Smith ORF**. Failure to Consult for Symptoms of Heart Failure in Patients with a Type D Personality. Heart 2007;93:814-8

2. Martens EJ, **Smith ORF**, & Denollet J. Psychological symptom clusters, psychiatric comorbidity and poor health status following myocardial infarction. Annals of Behavioural Medicine 2007;34:87-94

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About the author

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